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The American Journal of Medicine

Vol. XVII OCTOBER, 1954 No. 4

Editorial

What Are "Acids" and "Bases"? . . . . . ARNOLD S. RELMAN 435

Clinical Studies

Mechanics of Pulmonary Ventilation in Patients with Heart Disease
CYRUS C. BROWN, JR., DONALD L. FRY AND RICHARD V. EBERT 438

Using intraesophageal pressure, recorded by a specially designed balloon, as an index of intrathoracic pressure, the authors studied pressure-volume relationships in the lungs of normal human subjects and patients with heart disease, confirming older observations indicating alteration of the elastic forces in the lungs in heart disease; this, together with reduction in vital capacity, appears to be an important factor in the production of exertional dyspnea. Pressure-flow studies indicated that, in general, greater pressure was required in patients with heart disease to produce the same level of flow. This appears to reflect increased tissue friction, and may be an important factor in the dyspnea of "cardiac asthma."

Respiratory Acidosis in Patients with Emphysema
J. E. COHN, D. G. CARROLL AND R. L. RILEY 447

The authors begin with a general exposition of the meaning and mechanism of respiratory acidosis, due to alveolar hypoventilation, then describe the clinical characteristics and management of the acute and chronic forms of the disorder as seen particularly in patients with emphysema. The points made are illustrated by a detailed account of eight representative cases. The discussion is so adroitly oriented as to give both an excellent general perspective of the problem and specific practical pointers on management without recourse to mechanical respirators.

Respiratory Acidosis. 1. Effects of Decreasing Respiratory Minute Volume in Patients with Severe Chronic Pulmonary Emphysema, with Specific Reference to Oxygen, Morphine and Barbiturates
RUSSELL H. WILSON, WAYNE HOSETH AND MARY E. DEMPSEY 464

This study again makes clear the general sequence of physiologic events which make so hazardous the unconsidered administration of oxygen, morphine and barbiturates to patients with prolonged elevation of alveolar carbon dioxide tension due to pulmonary emphysema. Such agents are apt to depress the hypoxic stimulus to respiration and to accentuate already existent respiratory acidosis, sometimes with disastrous results.

A Physiologic Evaluation of the Effects of Diaphragmatic Breathing Training in Patients with Chronic Pulmonary Emphysema . . . . WILLIAM F. MILLER 471

The author made appropriate pulmonary function studies in twenty-four patients with chronic pulmonary emphysema before and after training in the modern technics of diaphragmatic breath-

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1939 — "Decholin...is much the best...to increase the flow of bile."
Hunter, C.: Canad. M. A. J. *30*:41 (Jan.) 1934.

1941 — *Decholin* may "...not only be applied as a therapeutic measure in all cases postoperatively, but...as an added step in the routine nonoperative management of gallbladder disease."
Best, R. R.; Hicken, N. F., and Finlayson, A. I.: Ann. Surg. *110*:67, 1939.

1946 — In chronic cholecystitis, "the bile acid of choice is dehydrocholic acid...."
Cheney, G., in Reimann, H. A.: Treatment in General Medicine, ed. 2, Philadelphia, F. A. Davis Company, 1941, vol. 1, p. 851.

1950 — "...Liberal quantities of Decholin...will be found advantageous in stimulating the flow of bile and promoting better drainage after operation."
Sanders, R. L.: Am. J. Surg. *72*:811, 1946.

1952 — "If the therapeutic aim is to flush the bile duct with a free-flowing, thin bile...dehydrocholic acid is administered...."
Cranshaw, J. F.: Am. J. Digest. Dis. *17*:387, 1950.

1953 — "...Decholin...does considerably increase the volume output of a bile of relatively high water content and low viscosity."
Beckman, H.: Pharmacology in Clinical Practice, Philadelphia, W. B. Saunders Company, 1952, p. 361.

"Dehydrocholic acid, because of its hydrocholeretic effect, increases the flow of dilute bile...."
O'Brien, G. F., and Schweitzer, I. L.: M. Clin. North America *37*:155 (Jan.) 1953.

AMES

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ing. The studies, which were carefully controlled, confirm the effectiveness of such exercises in increasing tidal volume at a lower respiratory rate. Clinical improvement was accompanied by such objective evidences of more adequate alveolar ventilation as increased O_2 removal rate, increased arterial oxygen saturation and decreased pCO_2. Since the diaphragmatic breathing exercises in question are simple and easily followed in the home, they should be more generally applied by the practitioner in the management of patients with indications of restrictive ventilation.

Chronic Bronchitis and Emphysema. Significance of the Bacterial Flora in the Sputum
CURTLAND C. BROWN, JR., MARION B. COLEMAN, RALPH D. ALLEY, ALLAN STRANAHAN AND C. H. STUART-HARRIS 478

The habitual presence of pathogenic or potentially pathogenic organisms in the respiratory tract in a significant proportion of patients with chronic bronchitis and emphysema is confirmed. H. influenzae and pneumococci were found particularly frequently. The inferences as to clinical significance and sites of persistent infection are discussed.

Pulmonary Arterial Hypertension with Markedly Increased Pulmonary Resistance. The Pulmonary Vascular Obstruction Syndrome
JOSEPH G. CUTLER, ALEXANDER S. NADAS, WALTER T. GOODALE, ROGER B. HICKLER AND ABRAHAM M. RUDOLPH 485

The authors take the position that, apart from what has been designated essential pulmonary hypertension, there is a more or less homogeneous group of cases of primary pulmonary hypertension due to intrinsic, possibly genetically determined obstruction of the peripheral pulmonary vasculature. This condition may or may not be associated with ventricular septal defects and other congenital cardiac anomalies; but if these are present and result in large left-to-right shunts, they may further contribute to hypertension in the pulmonary circuit, with secondary structural changes in the pulmonary vasculature. On the basis of seven rather heterogeneous cases, all having increased pulmonary vascular resistance in common, the clinical and hemodynamic characteristics of this syndrome are defined. Therapeutic implications, particularly in respect to corrective surgery of shunts, are indicated.

Effects of Diet in Essential Hypertension. III. Alterations in Sodium Chloride, Protein and Fat Intake
FREDERICK T. HATCH, ARTHUR R. WERTHEIM, GERALD H. EURMAN, DONALD M. WATKIN, HERMAN F. FROEB AND HANNAH A. EPSTEIN 499

This detailed study confirms previous findings that the essential antihypertensive principle of the Kempner rice-fruit regimen lies in its extremely low sodium content. Titration of the critical quantity of sodium which could be tolerated without loss of antihypertensive effect indicated that 0.5 gm. NaCl, and in some instances 1.0 gm. NaCl, could be added to the daily rice diet but that

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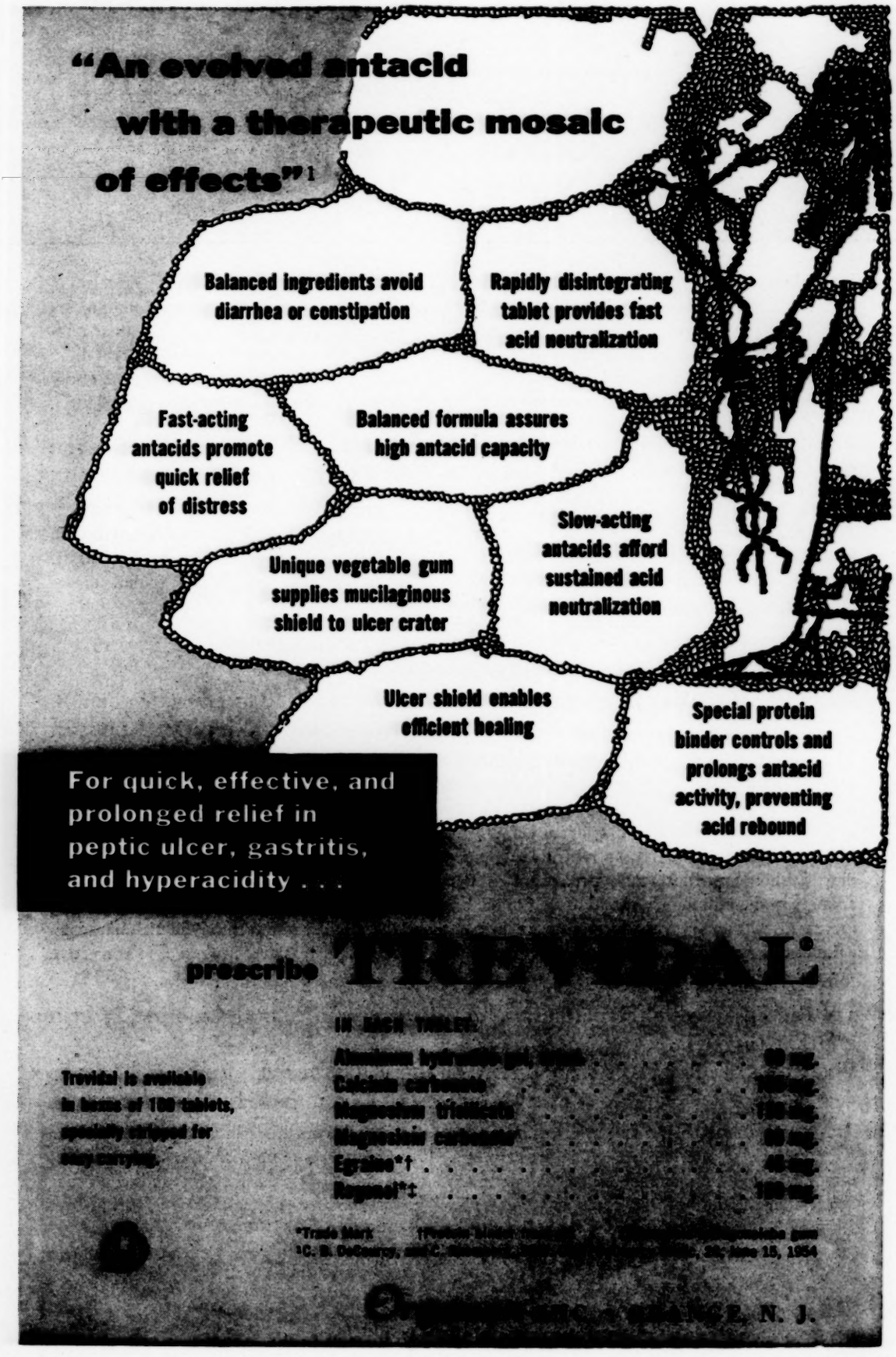
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addition of 3 gm. NaCl daily cancelled all antihypertensive action. Appreciable quantities of low-sodium protein, fat or carbohydrate could be added without adversely affecting the blood pressure response. A more diversified low-sodium diet, similar to others now in use, was devised based on these observations.

Hyperlipoproteinemia
JOHN W. GOFMAN, LEONARD RUBIN, JAMES P. MCGINLEY AND HARDIN B. JONES 514

Dr. Gofman and his colleagues have subjected to ultracentrifugal analysis the sera of patients with a variety of diseases all known to be accompanied by excessive lipids in the blood. Included in the study are a substantial number of cases of xanthoma tendinosum, xanthoma tuberosum, xanthelasma, nephrotic syndroma, biliary obstruction, myxedema and "essential" hyperlipemia. Each clinical entity appears to have its own characteristic serum lipoprotein spectrum in terms of S_f categories—an advance over the ordinary blood lipid fractionations, which revealed largely quantitative differences. Some of these serum lipoprotein anomalies give evidence of genetic transference, another indication that the disorders in question may reflect errors in lipoprotein rather than in lipid metabolism.

Serum Lipoproteins in Infectious Mononucleosis . . . . . LEONARD RUBIN 521

The data suggest that in infectious mononucleosis there is a decrease in S_f 0–12 serum lipoproteins and an increase in serum lipoproteins with flotation rates greater than S_f 12. These findings are quite different from those noted in infectious hepatitis, which may be indistinguishable on clinical grounds alone. The author goes on to speculate concerning the possible significance of ultracentrifugal serum lipoprotein fractionation in relation to the flocculation tests for liver disease.

Reviews

Spontaneous Subarachnoid Hemorrhage . . . . . GUY R. MCCUTCHAN 528

A concise but informative discussion, based chiefly on personal observations in twenty-one cases, of an entity frequently encountered but often poorly understood, spontaneous subarachnoid hemorrhage. Several points of interest are considered, among them the propriety of prophylactic surgical intervention in cases not associated with hypertension.

Renal Tuberculosis . . . . . JOHN K. LATTIMER AND ROLAND J. KOHEN 533

The authors here summarize a very large and carefully annotated experience with the use of antituberculous drugs in the management of renal tuberculosis, their observations extending over a five-year period. A variety of regimens was systematically investigated including the judicious use of surgery. The results are distinctly encouraging in what formerly was a dreaded late complication of pulmonary tuberculosis, even if arrested. The reader will find this an illuminating and rewarding contribution to this important subject.

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Seminars on Antihypertensive Drugs

Management of Arterial Hypertension . . . . . HENRY A. SCHROEDER 540

In this important paper Dr. Schroeder describes the current results of his present regimen for the management of arterial hypertension by use of antihypertensive drugs. After explaining the rationale for use of hexamethonium chloride and 1-hydrazinophthalazine in combination, he gives a detailed account of the results of their (oral) administration in 304 consecutive hypertensive patients selected only because they represented severe forms of the condition. Some also received reserpine. The figures in respect to prolonged control of hypertension are impressive and deserve careful study. With reduction in hypertension, there was striking improvement in symptoms, eye-ground changes, congestive failure, cardiac enlargement and other expressions of the hypertensive state. Renal insufficiency and occlusive vascular changes, however, proved to be irreparable. The regimen requires persistence, attention to detail and a variety of precautions, and is not without hazard, but would certainly seem to justify more extensive trial.

Clinico-pathologic Conference

Fever, Lethargy, Pericarditis and Sudden Death. 562

Clinico-pathologic Conference (Washington University School of Medicine)—The sequence of clinical events in this case was puzzling even though the findings at postmortem examination were straightforward. The protocol illustrates how difficult diagnosis may be in elderly patients with diffuse degenerative changes in the vascular tree.

Case Reports

Spontaneous Rupture of the Esophagus. With a Note on Tissue Necrosis from Norepinephrine . . . . C. WARREN IRVIN, JR. AND GEORGE H. BUNCH, JR. 571

"Spontaneous" rupture of the esophagus, with acute mediastinitis, represents an emergency requiring prompt diagnosis and quick and effective management. This interesting report describes two typical cases and reviews the present status of therapy in this disorder.

The Taussig-Bing Syndrome. A Report of Two Further Cases, One Complicated by Aortic Coarctation . . GEORGE G. MAXWELL AND CHARLES W. CRUMPTON 578

Two cases are presented of a rare cardiac anomaly: origin of the aorta entirely from the right ventricle, the pulmonary artery arising from the left chamber and straddling a ventricular septal defect (Taussig-Bing syndrome). One of these cases also had an almost complete coarctation of the aorta between the left common carotid and the left subclavian artery, with patent ductus; associated with this was deep cyanosis of the right upper extremity, absent pulse on the left.

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references: 1. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, March 22, 1952. 2. Boland, E. W.: M. Clin. North America. Philadelphia and London, W. B. Saunders Company, March, 1954, p. 337.

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Plasma Cell Leukemia or Multiple Myeloma with Osteosclerosis
J. G. SHARNOFF, H. BELSKY AND J. MELTON 582

An unusually interesting case of what would appear to be multiple myeloma with many myeloma cells in the peripheral blood, associated with diffuse, dense osteosclerosis. The question raised is whether the presence of osteosclerosis would not be more compatible with a true plasma cell leukemia.

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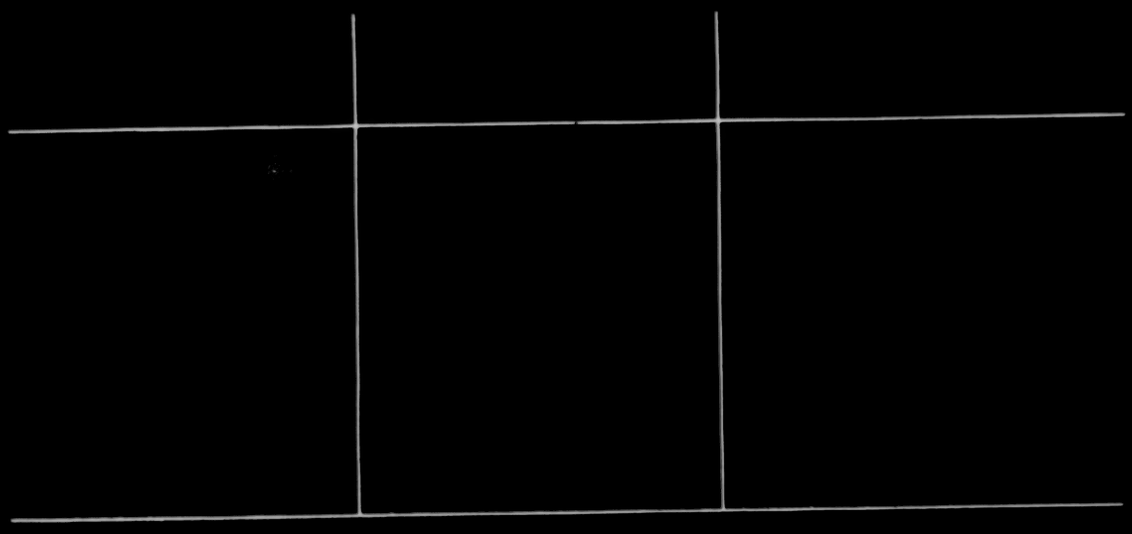

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1. Kloha, M.W.; Draper, M. D., and Keller, F.: J. Am. Chem. Soc. *76*:2843 (May 20) 1954.
2. Cronheim, G.; Brown, W.; Cawthorne, J.; Toekes, M. I., and Ungari, J.: Proc. Soc. Exper. Biol. & Med. *86*:110 (May) 1954.

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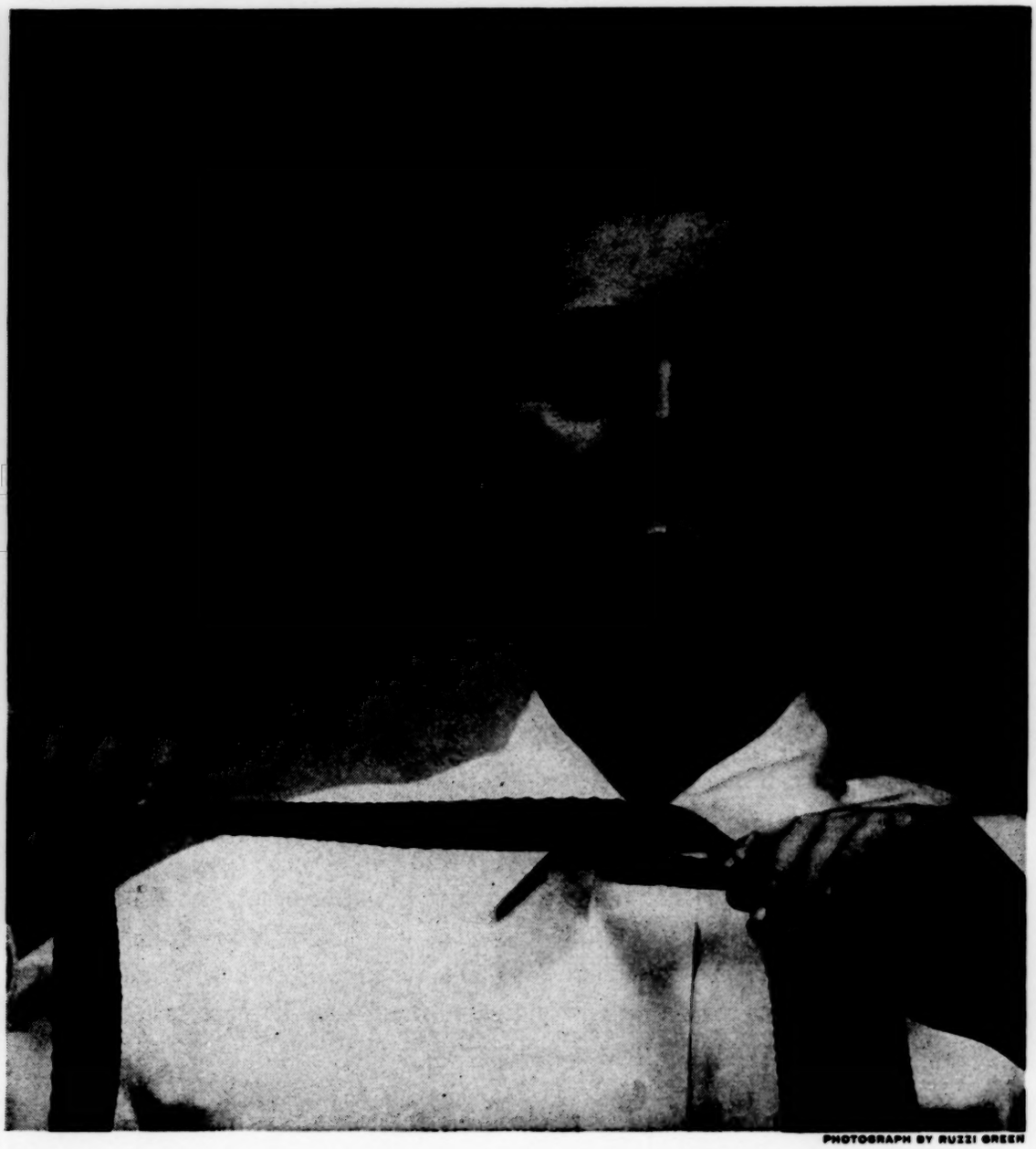

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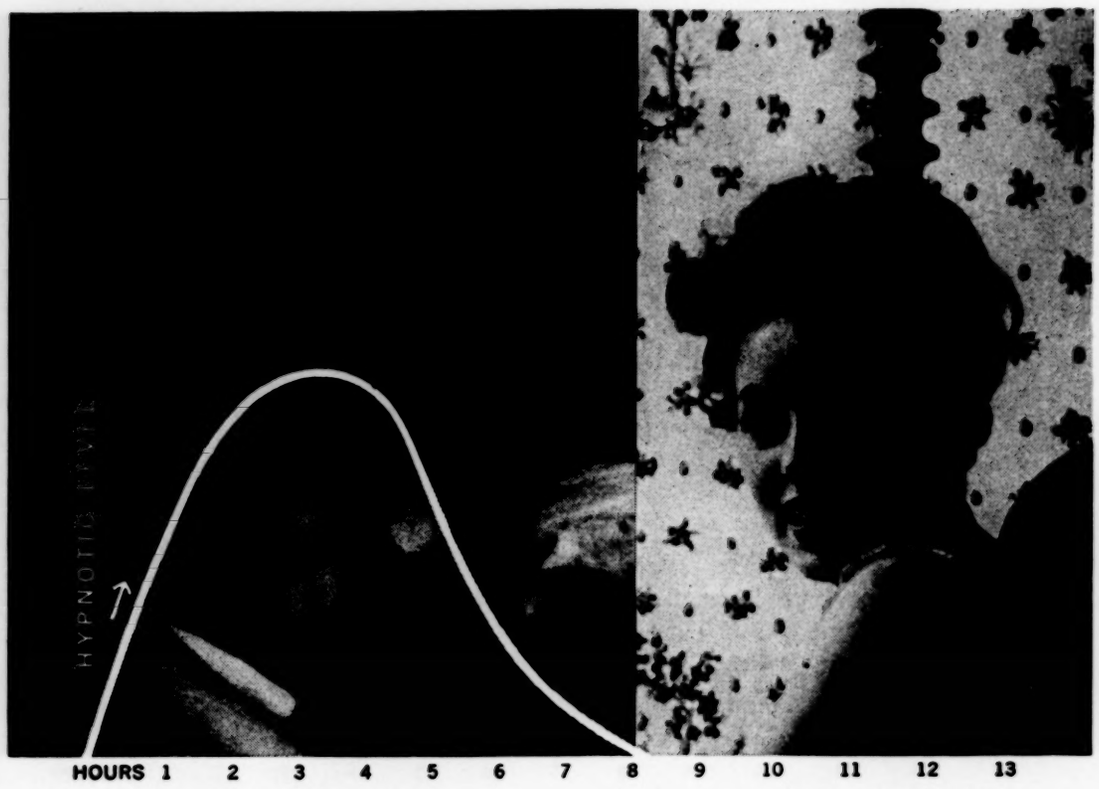

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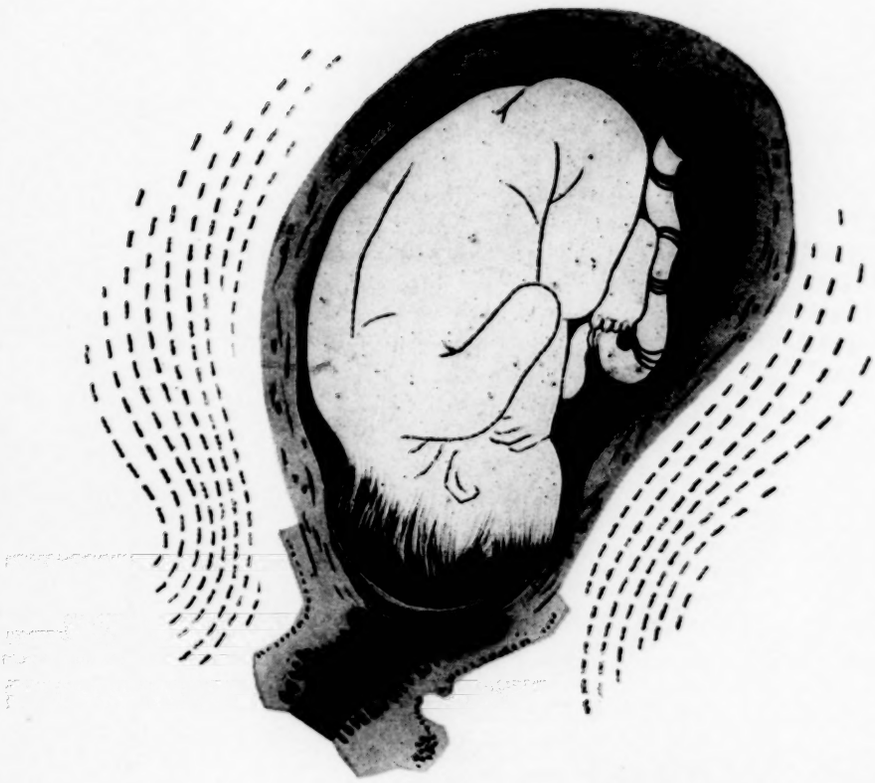

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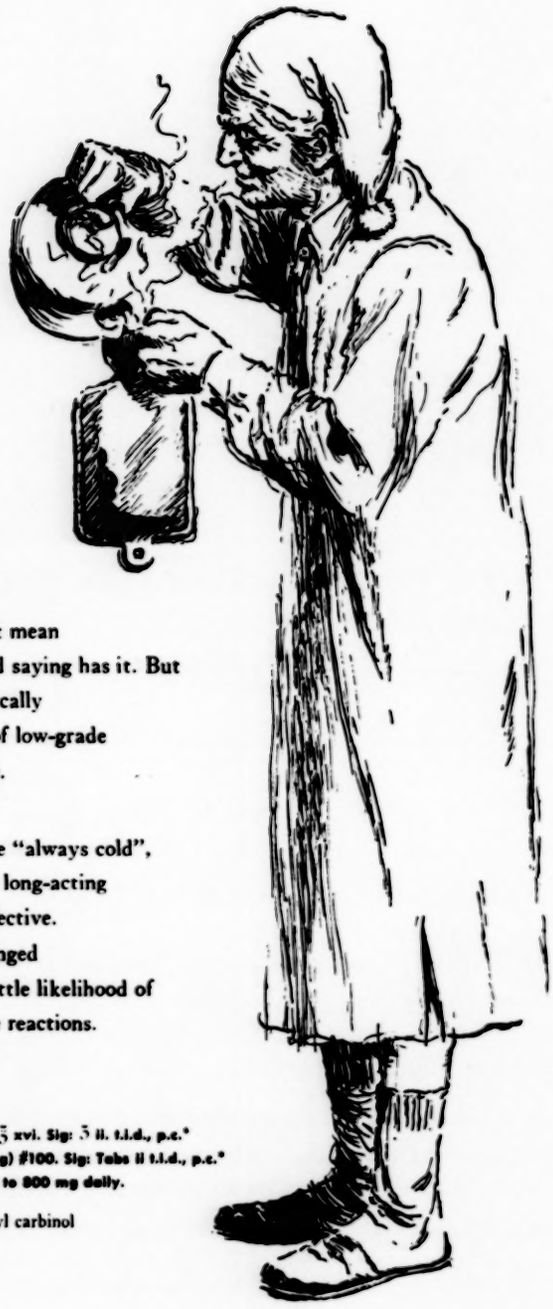

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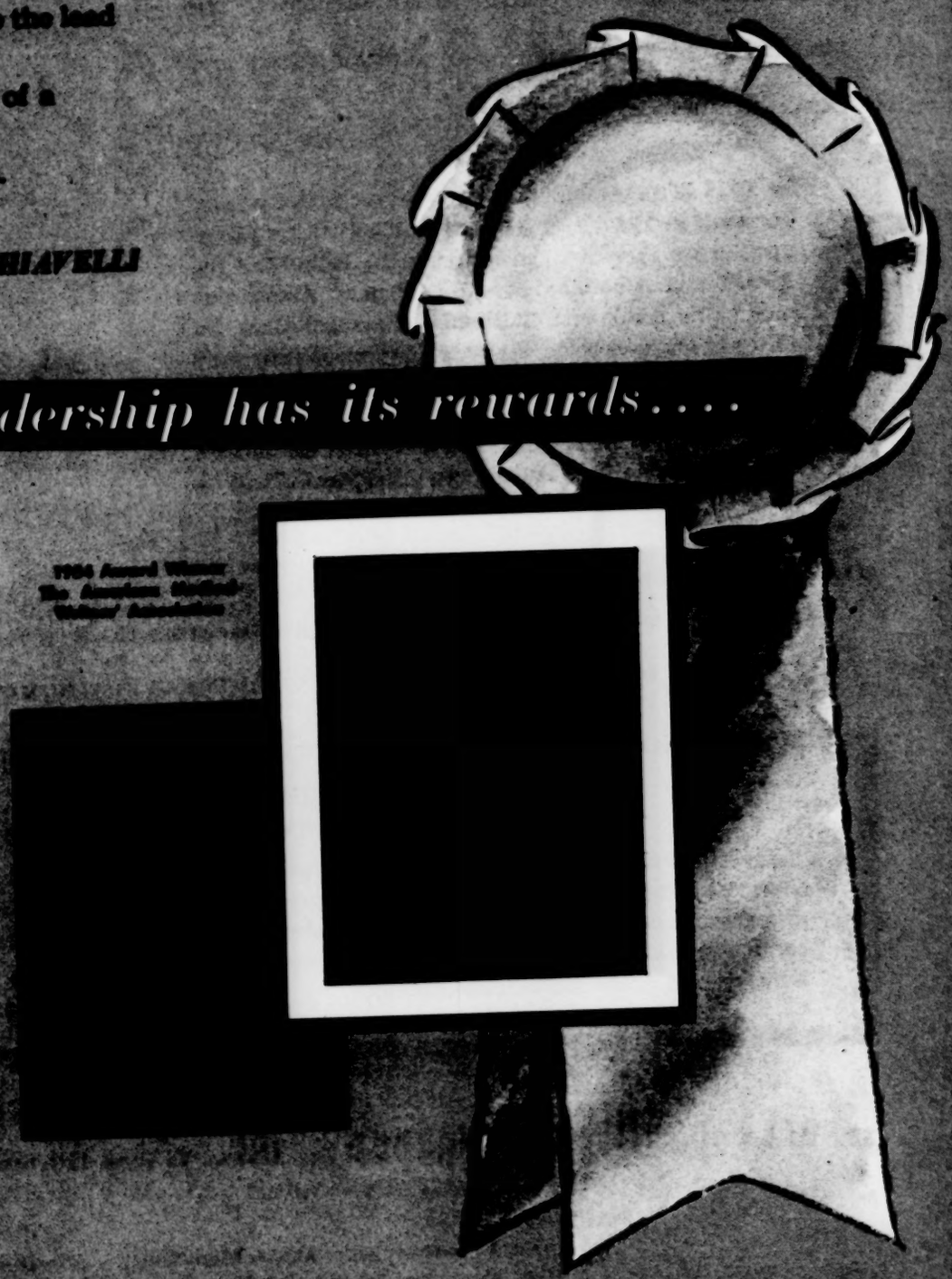

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* Wilkins, R. W.; Judson, W. E.; Stone, R. W.; Hollander, William; Huckabee, W. E., and Friedman, I. H.: Reserpine in the Treatment of Hypertension: A Note on the Relative Dosage and Effects, New England J. Med. 250:477 (March 18) 1954.

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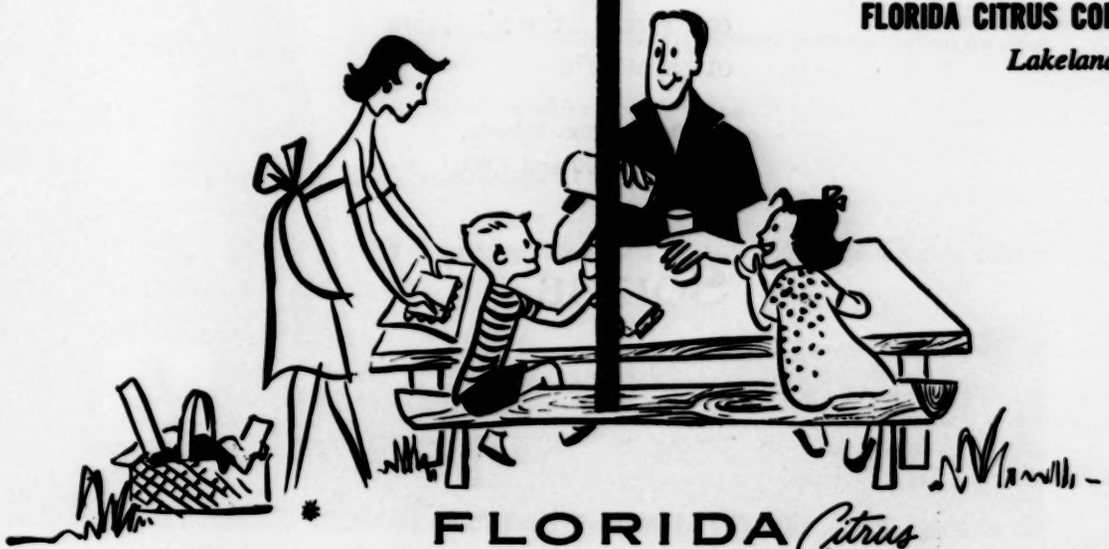

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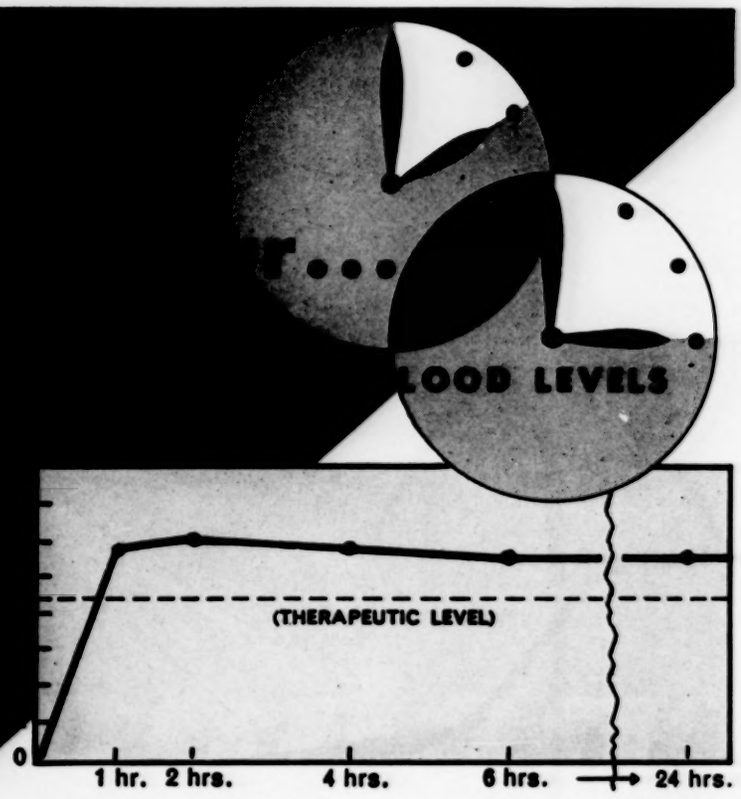

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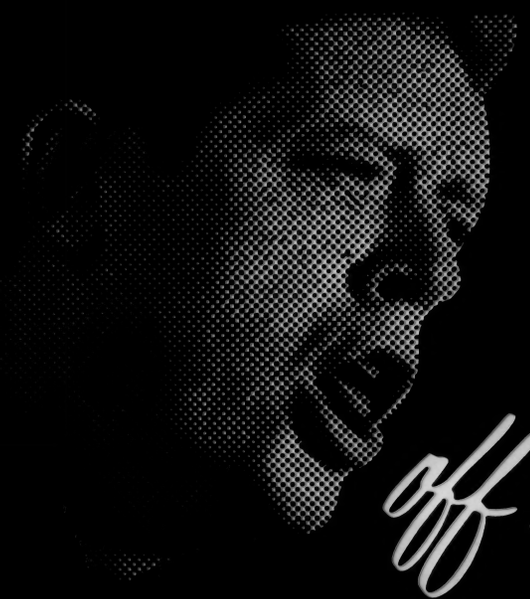

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VOL. XVII OCTOBER, 1954 No. 4

Editorial

What Are "Acids" and "Bases"?

EVERYONE agrees that acid-base metabolism has to do with the mechanisms determining the reaction of body fluids but there appears to be considerable confusion over the use of the terms, "acid" and "base." For the past few decades most non-clinical chemists have been fairly well agreed that an "acid" is any substance with an available proton, or hydrogen ion, and a "base" is any substance with a capacity to bind or accept protons. The free acidity or alkalinity of solutions (including plasma, urine and the tissue fluids) is measured by the concentration and activity of hydrogen ions.

In the literature of clinical chemistry a different and somewhat bewildering nomenclature is encountered. Here "base" appears to mean any cation, such as sodium (Na^+), potassium $(K)^+$, calcium (Ca^{++}), magnesium (Mg^{++}) or ammonium (NH_4^+), and "acid" refers to any anion, such as chloride (Cl^-), phosphate ($HPO_4^=$, $H_2PO_4^-$), or sulfate ($SO_4^=$). In this system the bicarbonate anion, (HCO_3^-), occupies a rather anomalous position because it is referred to both as an "acid radical" and as the "alkali-reserve" of the blood. This terminology entirely neglects the central position of the hydrogen ion in acid-base reactions.

The origin of this confusion is to be found in the history of modern chemistry. By the late eighteenth century it had become customary to divide the common inorganic compounds into (1) substances with acid properties, (2) those with alkaline properties, which could neutralize acids and (3) neutral salts which resulted from the union of acids with alkalis. It was also known that the oxides of the so-called alkali-metals such as sodium, potassium and calcium formed alkaline solutions, whereas chlorine and the oxides of sulfur or phosphorus tended to make water acidic. Then about one hundred fifty years ago several workers, including Sir Humphry Davy and J. J. Berzelius, discovered that passage of an electric current through inorganic compounds decomposed them into their constituent parts. In solutions of the common neutral salts, metals such as sodium and potassium and calcium were concentrated at the negative pole and the liquid nearby became alkaline. At the opposite or positive pole such elements as chlorine, sulfur or phosphorus were recovered and the liquid near them became acid in reaction. Electrical decomposition of acids resulted in the recovery of only these latter elements, while similar treatment of the common alkalis resulted in the isolation of the alkali-metals. Thus appeared the custom of calling the alkali-metals "base-forming" or "basylous" elements, and elements such as sulfur, chlorine and phosphorus "acid-forming" or "acidulous." Faraday's description of the processes of electrolysis in terms of "cations" and "anions" provided the final step necessary for the general adoption of this terminology: cations were called "base-formers" and anions "acid-formers." Salts consisted of a combination of a cation or "base-residue" with an anion or "acid-residue."

It was not until the late nineteenth century that new advances in the theory of ionization and chemical equilibria, particularly the work of Svante Arrhenius, made it necessary to revise and broaden the conception of acid and base. Prior to this time it was known that hydrogen was an essential constituent of acids, and that many alkaline substances contained –OH groups, but the general significance of these facts for the theory of acid-base reactions was not appreciated. Beginning about 1890 rapid changes in acid-base theory took place. Acids and bases were re-defined in terms of their ability to furnish hydrogen or hydroxyl ions in aqueous solutions. In 1923 Brønsted suggested the cur-

rently accepted definitions. It is now recognized that the essential process in all acid-base reactions is the transfer of protons, and that proton-donators (acids) and proton-acceptors (bases) may be anions or cations, or they may be non-ionized compounds. According to the view of the present day physical chemist, chloride and sulfate anions are not acids at all but rather extremely weak bases. The alkali-metal cations such as sodium and potassium are neither acids nor bases. The ammonium cation is a weak acid, not a base; and, at the pH of blood, the bicarbonate anion is a weak base but the dihydrogen phosphate anion is a weak acid.

While these advances in physicochemical theory were occurring, the old cation-anion definitions of acid and base had become firmly entrenched in the new and growing literature of physiologic and medical chemistry. At the turn of the century one finds this terminology appearing in the standard clinical chemistry textbooks of the day (e.g. Bunge[1] and Witthaus[2]) and in the writings of the pioneer workers in the field (e.g., Folin,[3] Sherman[4] and L. J. Henderson[5*]). The early clinical chemists were apparently responsible for one final modification in terminology. Presumably for the sake of brevity, they began the custom of referring to the "acid-forming" elements, or their anions, simply as "acids" and to the "base-forming" elements, or their cations, as "bases." The tradition, once established, has been carried down to the present by almost all subsequent writers in the field of clinical acid-base physiology.

It would seem, therefore, as if the clinical chemists have persisted in using a set of acid-base definitions which is totally at variance with the language of most other branches of present day chemistry and which appears to have considerably more historic than scientific justification. This practice is particularly puzzling in view of the fact that the central role of the hydrogen ion in the buffering processes regulating the neutrality of the blood was first demonstrated over forty years ago by L. J. Henderson[6] and subsequently accepted by all clinical chemists. With the consistent use of the old-fashioned definitions of "acid" and "base" it is virtually impossible to give an accurate description of these hydrogen-transfer processes, or to describe the titration of any buffer. The old terminology makes descriptions of the renal regulation of acid-base balance equally unsatisfactory.

The complications resulting from this semantic schism have disturbed a number of authorities. Fifteen years ago Shohl[7] felt obliged to comment that "there has been a good deal of confusion in writing about the acid-base economy of the body because of the looseness of terms used." Clark in his recent textbook[8] reviews the diverse origins of acid-base terminology and notes "how ambiguous have become some of the more commonly used terms." Hitchcock[9] remarks that "the term 'base' . . . has been used in quite different and contradictory meanings." Several other authors of new textbooks comment in a similar vein. A particularly cogent criticism of clinical acid-base terminology has been made recently by Christensen, who points out that the use of a language which neglects the central role of the hydrogen ion has resulted in a "separation of some of the terminology in this field from conceptions of what actually happens."[10]

Granting that clinical acid-base terminology is anachronistic, the question still remains whether it would be prudent to attempt changing definitions so well established by custom and long usage. Would not such an innovation simply result in more misunderstanding and confusion? "Usage and not the reformer," observes Dr. Clark,[8] "is the arbiter of words and figuratively writes the dictionary."

[1] Bunge, G. Textbook of Physiological and Pathological Chemistry, 2nd English ed. Philadelphia, 1902. P. Blakiston's Son and Co. Inc.

[2] Witthaus, R. A. The Medical Student's Manual of Chemistry, 5th ed. New York, 1902. Wm. Wood and Co.

[3] Folin, O. The acidity of urine. *Am. J. Physiol.*, 9: 265, 1903.

[4] Sherman, H. C. and Sinclair, J. E. The balance of acid-forming and base-forming elements in foods. *J. Biol. Chem.*, 3: 307, 1907.

[5] Henderson, L. J. The excretion of acid in health and disease. *The Harvey Lect.*, Series X, pp. 132–153, 1914–1915.

* Henderson referred to the cations of biologic fluids as "bases," but he reserved the term "acid" for compounds supplying hydrogen ions.

[6] Henderson, L. J. The theory of neutrality regulation in the animal organism. *Am. J. Physiol.*, 21: 427, 1908.

[7] Shohl, A. T. Mineral Metabolism (American Chemical Society Monograph Series), p. 274. New York, 1939. Reinhold Publishing Corp.

[8] Clark, W. M. Topics in Physical Chemistry, pp. 240–241. Baltimore, 1948. Williams and Wilkins.

[9] Hitchcock, D. I. Physical Chemistry for Students of Biology and Medicine, 4th ed., p. 68. Boston, 1953. Little, Brown and Co.

[10] Christensen, H. N. Control of the hydrogen ion. *New England J. Med.*, 247: 174, 1952.

One answer to this argument is that the traditional definitions have already been the source of too much confusion and that continued use of contradictory and inaccurate language in science, however familiar the terms may be, can lead only to more and more misunderstanding.

Lewis Carroll seems to have epitomized the problem very neatly:

> "When *I* use a word," Humpty Dumpty said in rather a scornful tone, "it means just what I choose it to mean—neither more nor less."
>
> "The question is," said Alice, "whether you *can* make words mean different things."
>
> *Through the Looking Glass*

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Clinical Studies

The Mechanics of Pulmonary Ventilation in Patients with Heart Disease*

CYRUS C. BROWN, JR., M.D., DONALD L. FRY, M.D. *and* RICHARD V. EBERT, M.D.
Minneapolis, Minnesota *Bethesda, Maryland* *Chicago, Illinois*

DYSPNEA is the most important symptom of heart failure. Peabody[1] observed that patients with heart failure developed dyspnea at levels of ventilation which lead to no discomfort in a normal person. He was also able to correlate the severity of exertional dyspnea with the degree of reduction of vital capacity.[2] The implication of these observations is that there is not only an increase in the level of pulmonary ventilation at rest or with a given degree of exertion in patients with heart failure as contrasted with normal individuals but also an alteration in the mechanics of ventilation. There have been relatively few studies of the mechanics of ventilation in patients with heart disease. Christie[3,4] demonstrated that there were greater fluctuations in intrathoracic pressure in patients with heart disease than in normal persons and attributed this to decreased distensibility of the lungs. Recently Mead and co-workers[5] have studied the mechanics of ventilation more completely and have concluded that there is an alteration in the elastic properties of the lung and an increase in resistance to motion of the lungs. The purpose of the present study is to analyze further the mechanics of ventilation in patients with dyspnea associated with disease of the heart.

METHOD

To evaluate the mechanics of ventilation in patients with heart disease the various pressure increments comprising the intrathoracic pressure were measured.

A general equation expressing the relationship of the pressure components making up the intrathoracic pressure may be written as:

$$P_T = P_L + P_V + P_P \quad \text{(Equation 1)}$$

where P_T is the intrathoracic pressure, P_L is the pressure caused by the retractive forces of the lung, P_V is the pressure required to overcome tissue friction of the lung and P_P is the pressure drop required to produce gas flow along the bronchial tree. P_V and P_P are related to movement of the lung and will be zero under static conditions. Therefore, at zero flow, equation 1 may be rewritten as follows:

$$P_T = P_L \quad \text{(Equation 2)}$$

The magnitude of P_L varies with the degree of lung inflation.

Equation 1 also may be rewritten as follows:

$$P_T - P_L = P_V + P_P \quad \text{(Equation 3)}$$

Thus the intrathoracic pressure less the elastic pressure equals the pressure required to overcome resistance to gas flow and tissue friction.

In this study the intraesophageal pressure was recorded from a specially designed balloon. This method has previously been shown to measure accurately changes in intrathoracic pressure.[6] Interruption of gas flow to bring about static conditions or zero flow was achieved by means of either a hand-operated three-way respiratory valve or an electrically operated solenoid valve. The differential pressure between the oral cavity and the esophagus represented the intrathoracic pressure and was recorded by means of a differential strain gauge. This dif-

* From The Department of Medicine, Medical School, University of Minnesota, The Variety Club Heart Hospital and the Veterans Administration Hospital, Minneapolis, Minn. This study was supported in part by a grant from The Minnesota Heart Association. Published with the approval of Chief Medical Director, Veterans Administration. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

ferential pressure, P_T, immediately before closure of the valve represented $P_L + P_V + P_P$ (Equation 1). The differential pressure after closure of the valve represented P_L (Equation 2). The difference between the pressure recorded immediately prior to the closure of the valve and the pressure recorded after closure represented $P_V + P_P$ (Equation 3). This assumes there was no change in lung volume during the time required for closure of the valve and that the glottis remained open. A spirometer tracing of volume changes of the lung was recorded at the same time, allowing correlation of P_L with the volume of the lung at the time of valve closure. By taking measurements at different lung volumes a pressure-volume diagram could be constructed. Simultaneous measurement of the rate of gas flow was recorded by means of a pneumotachygraph. By measuring $P_V + P_P$ at different levels of gas flow a pressure-flow diagram could be constructed. The complete details of this method have been described previously.[7,8]

To differentiate the two components of frictional resistance, P_V and P_P, it was necessary to have the subjects breathe two gases with different physical properties but which had about equal kinematic viscosities. The gas mixtures used were air, and 80 per cent argon with 20 per cent oxygen. The rationale for the use of this procedure is that any difference in the pressure-flow relationship while one mixture is breathed as compared with the pressure-flow relationship when another gas mixture is breathed must be attributable to the different physical properties of the two gas mixtures since tissue friction is independent of the gas breathed. The reasons for the selection of these particular gas mixtures have been explained in detail elsewhere.[7] By means of a mathematical analysis of the data obtained it was possible to estimate the magnitude of P_V.

In this study the three pressure components, P_L, P_V and P_P, were evaluated in patients with heart disease. The results are divided in two parts: Part I deals with the measurement of P_L and Part II deals with the measurement of P_V and P_P.

RESULTS

Part I. Before considering the elastic properties of the lungs of patients with heart disease it is desirable to describe the nature of these forces in normal subjects. As might be expected the retractive force of the lung varies with the volume of the lung. A pressure-volume diagram can be constructed by plotting the retractive force, P_L, against the volume of the lung. Such a curve is illustrated in Figure 1. It will be noted that the curve is essentially linear in the range of the functional residual volume but shows considerable curvature at the higher levels of lung volume. The elastic properties of the lung would be expressed most accurately by the equation of this curve. For practical purposes, however, only the relatively linear portion of the curve in the region of the functional residual volume was analyzed. The slope of this line was expressed in terms of the pressure change required to produce a change of 100 cc. in the volume of the lung. In a previous study of the elastic properties of the lungs of normal men a mean value of 0.43 cm. of water pressure change per 100 cc. change in lung volume was found.[8] In the present study the elastic properties of the lungs of six normal women were studied. A mean value of 0.60 cm. of water pressure per 100 cc. change in lung volume was found. (Table I.) The reciprocal of the vital capacity of the normal men and women was

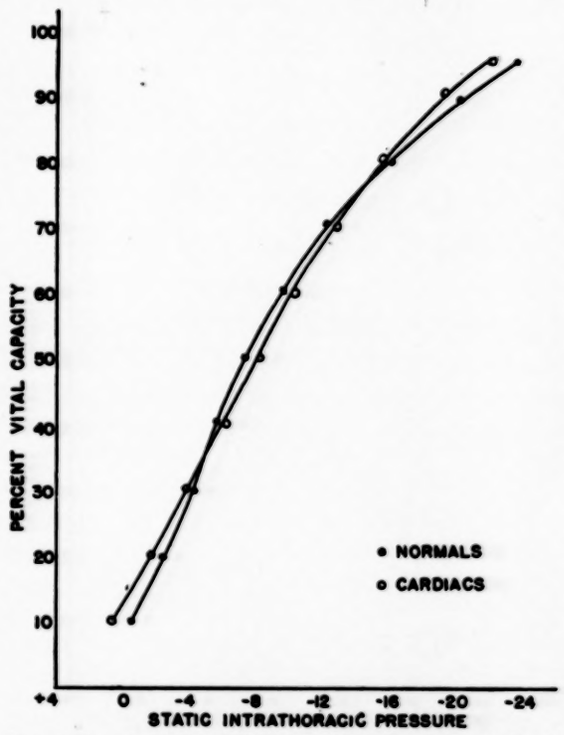

FIG. 1. Comparison of the mean elasticity curves of normal subjects and of patients with heart disease. The normal curve represents the combined mean curves for both men and women. The vital capacity is expressed in per cent of the measured vital capacity for each individual. The intrathoracic pressure is expressed in cm. of H_2O and is related to atmospheric pressure.

plotted against the pressure change per 100 cc. change in lung volume. (Fig. 2.) As can be seen, a high degree of correlation exists between these two variables (r = .67). A similar relationship has been described by Mead.[5] It thus appears that the retractive force of the lung in normal men and women is closely related to the size of the vital capacity.

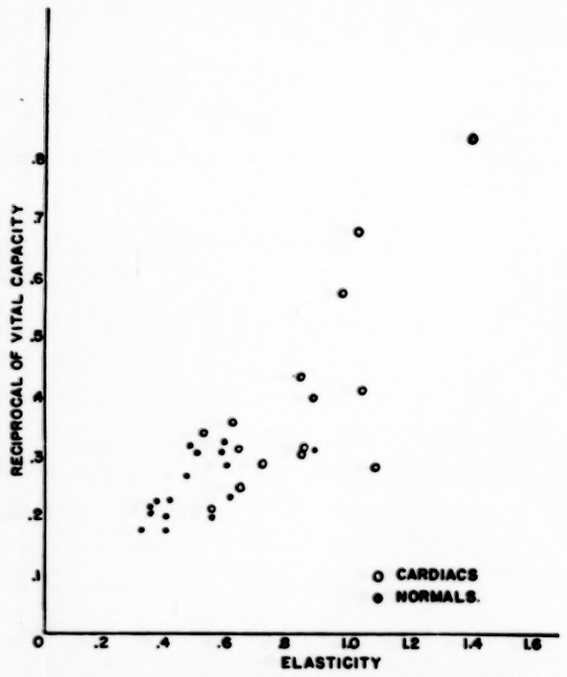

FIG. 2. The correlation of the lung elasticity (expressed as the pressure change per 100 cc. change in lung volume) and the reciprocal of the vital capacity (L.) in normal subjects and patients with heart disease.

To evaluate the elastic properties of the lungs of patients with heart disease, fifteen patients with heart disease of different etiologies and varying degrees of severity were studied. (Table II.) The usual criteria for the establishment of the presence of heart disease were employed. Patients who showed clinical or laboratory evidence of pulmonary emphysema were excluded from the study.

A pressure-volume diagram was constructed for each patient. These curves were, in general, similar in shape to the curves obtained in normal subjects. (Fig. 3.) The change in pressure per 100 cc. change in lung volume in patients with heart disease was 0.84, which is significantly greater than that found in the normal subjects (p = .01). Again, the reciprocal of the vital capacity was plotted against the pressure change per 100 cc. change in lung volume. As can be seen from Figure 2, there is high correlation between not only the patients with heart disease as a group (r = .77) but also between these patients and the normal subjects.

This correlation suggested that a relationship exists between the vital capacity and the elastic forces of the lungs. To elucidate this relationship further, the static intrathoracic pressure, P_L, was plotted against the level of lung inflation expressed in terms of the per cent of the vital capacity. As can be seen in Figure 1 the curve for the normal subjects and the curve for patients with heart disease are essentially identical when plotted in this manner. This further substantiates the existence of a close relationship between the vital capacity and the elastic forces of the lungs and suggests that the reduction in vital capacity in patients with heart disease is a result of an alteration in the elastic properties of the lung.

TABLE I

STUDIES ON THE ELASTIC PROPERTIES OF THE LUNGS IN NORMAL WOMEN

Case No.	Sex and Age	Vital Capacity (cc.)	Total Lung Volume (cc.)	Change in Intraesophageal Pressure in cm. H_2O per 100 cc. Change in Lung Volume	Intraesophageal Gauge Pressure at the Functional Residual Volume (cm. of H_2O)
1	F, 24	3,200	4,590	0.90	9.6
2	F, 25	3,140	3,710	0.46	4.5
3	F, 22	3,680	4,060	0.46	1.8
4	F, 24	3,500	4,660	0.60	5.2
5	F, 23	3,080	4,590	0.59	8.6
6	F, 24	3,220	4,300	0.58	7.1
Mean, normal women	23.7	3,303	4,320	0.60	6.1
Mean, 10 normal men	31.7	4,689	6,250	0.43	6.02

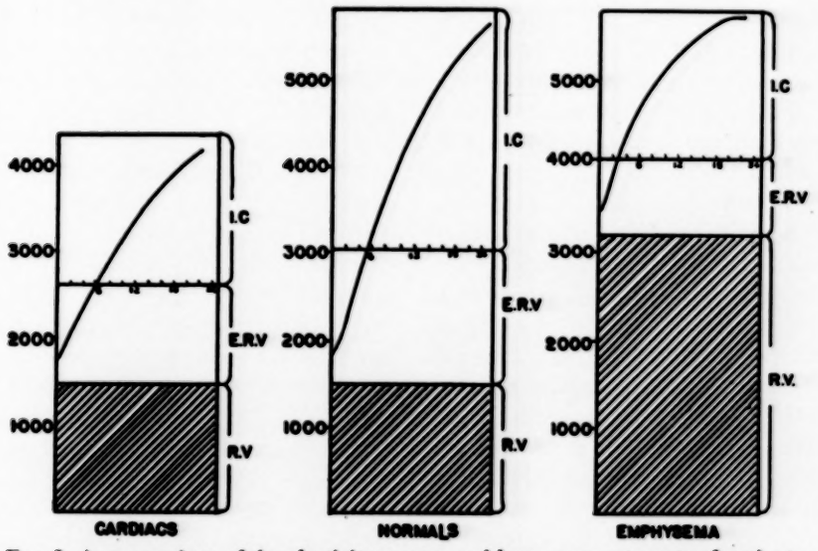

FIG. 3. A comparison of the elasticity curves and lung compartments of patients with heart disease, normal subjects and patients with pulmonary emphysema. Symbols: R.V = residual volume; E.R.V = expiratory reserve volume; I.C. = inspiratory capacity. The lung compartments are expressed in cc. and the pressure in cm. of H_2O.

TABLE II

STUDIES ON THE ELASTIC PROPERTIES OF THE LUNGS IN PATIENTS WITH HEART DISEASE

Case No.	Type of Heart Disease	Sex and Age	Surface Area (sq. m.)	Vital Capacity (cc.)	Total Lung Volume (cc.)	Change in Intraesophageal Pressure in cm. H_2O per 100 cc. Change in Lung Volume	Intraesophageal Gauge Pressure at the Functional Residual Volume (cm. of H_2O)
1	RHD	M, 18	1.90	3,490	5,530	1.09	7.2
2	RHD	F, 44	1.46	2,410	4,084	....	....
3	RHD	F, 43	1.55	2,000	2,987	....	....
4	RHD	M, 31	1.75	4,010	5,891	0.64	9.9
5	HCD	F, 65	1.49	1,200	2,739	1.40	4.6
6	IHD	F, 54	1.59	2,260	3,607	1.04	3.0
7	RHD	M, 43	1.69	2,500	4,174	0.89	3.6
8	RHD	M, 49	2.03	2,810	....	0.61	1.1
9	HCD	M, 35	1.97	3,100	5,009	0.85	13.0
10	AHD-HCD	F, 53	1.67	1,600	....	1.03	2.7
11	RHD	F, 40	1.66	1,740	3,364	0.98	3.0
12	RHD	M, 55	1.92	3,210	5,098	0.64	8.0
13	RHD	M, 31	1.75	3,400	5,260	0.71	8.4
14	RHD	M, 55	1.67	3,250	5,327	0.84	5.5
15	RHD	M, 39	1.80	2,970	3,810	0.52	4.3
16	RHD	F, 32	1.82	2,310	4,030	0.84	8.3
17	RHD	M, 44	2.16	4,720	7,190	0.55	9.1
Means	.....	43	1.76	2,760	....	0.84	6.1

RHD = Rheumatic heart disease.
HCD = Hypertensive cardiovascular disease.
AHD = Arteriosclerotic heart disease.
IHD = Idiopathic heart disease.

Since the retractive force of the lung is a function of the absolute volume of the lung, the lung elasticity curve should be considered in relationship to the lung compartments. In Figure 3 the lung compartments for normal subjects, patients with heart disease and a patient with pulmonary emphysema, together with their respective elasticity curves, are illustrated. The residual air in patients with heart disease is essentially the same as in normal subjects while the vital capacity and total lung volume are reduced. This is in contrast to the patient with emphysema who has an increased residual volume, a decreased vital capacity and a normal total lung volume. These changes in the lung compartments are similar to those described previously by others.[9–11] If the retractive force of the lung, P_L, is compared with the absolute degree of lung inflation, it will be noted that for the most part at identical levels of lung inflation the elastic force is less in the patient with emphysema than in the normal subjects while in the patients with heart disease the elastic force is increased.

It is clear from these studies that there is an alteration in the elastic properties of the lungs of patients with heart disease in association with a diminution of vital capacity. This alteration has been described by previous investigators. Christie and Meakins,[3] using intrapleural pressure as a method of measuring intrathoracic pressure, noted that an increased pressure was required to produce a given change in lung volume in patients with heart disease as compared with normal subjects. However, their method did not distinguish between the elastic forces of the lung and the resistance to air flow. Mead, Frank, Lindgren, Gaensler and Whittenberger,[5] using intraesophageal pressure as a measure of intrathoracic pressure, described results similar to those found in the present study.

A number of explanations must be considered for the alteration of the elastic forces and the diminution of vital capacity in patients with heart disease. One possible explanation is that the volume of the thoracic space is reduced by such factors as a large heart, pleural effusion and elevation of the diaphragm associated with enlargement of the liver and ascites.[10,11] If this were the correct explanation one would expect the pressure change required to produce a given volume change in the lungs to be the same as in normal subjects and that the intrathoracic pressure at the functional residual volume would be less negative. This is because diminution in the volume of the thoracic space would lead to a reduction in the volume of the lung but would not alter the elastic properties of the lung. The observations made in this study do not support this hypothesis.

A second explanation is that an alteration in pulmonary blood volume is responsible for the altered retractive forces of the lung. There is considerable evidence in the literature to support this hypothesis.[12–21] It has been shown repeatedly that an increase in vital capacity is produced by venesection or by procedures which pool blood in the extremities. It has been postulated that the mechanism of this alteration in vital capacity is a decrease in the volume of blood in the lungs. Furthermore, in animal experiments the production of an increase in pulmonary blood volume leads to an alteration in the elastic properties of the lung.[12,13] The mechanism whereby an alteration in pulmonary blood volume produces these changes is less clear. It has been suggested that the reduction in vital capacity associated with an increase in pulmonary blood volume is caused by encroachment on the volume of the alveolar space by distended blood vessels and that the decrease in total amount of air in the lungs is equivalent to the amount of the increase in pulmonary blood volume.[11,12,17,19] Measurements of pulmonary blood volume in patients with mitral stenosis have not confirmed this theory since increases of pulmonary blood volume of this magnitude were not found.[22–24] Another and more likely theory was suggested by von Basch.[25] This theory postulates that there is an increase in the rigidity of the lung tissues as a result of increase in the pulmonary capillary pressure in the lungs of patients with heart disease. An additional factor which would contribute to this alteration of the elastic properties of the lung tissues is interstitial edema secondary to the increased pulmonary capillary pressure.

It appears likely that the alteration in the elastic forces of the lungs in patients with heart disease is an important factor in the production of dyspnea. It has been shown by Peabody,[1] Harrison[26] and Barr and Peters[27] that patients with heart failure and a reduction in vital capacity develop dyspnea at a level of ventilation which does not produce discomfort in a normal subject. This implies that there is an alteration in the mechanics of ventilation which plays an important role in the production of the subjec-

tive sensation of dyspnea. It has been demonstrated in this study that in patients with heart disease a greater change in intrathoracic pressure is required to produce a given change in lung volume than in normal subjects. This means that at any given level of tidal volume more work is required during inspiration than is the case in normal individuals. While it would seem clear that the symptom of dyspnea is related to these alterations in the mechanics of ventilation, the exact mechanism of production of this sensation and the sensory receptors are not known.

Part II. In a recent publication the various factors contributing to the frictional resistance associated with movement of the lungs of normal human beings and patients with pulmonary emphysema were discussed in detail.[7] The three basic components which comprise this resistance are: the pressure required to overcome resistance to laminar gas flow, the pressure required to overcome resistance to turbulent gas flow and the pressure required to overcome tissue friction. It was shown that all the frictional resistance to movement of the lungs was due to laminar and turbulent gas flow and that tissue friction was a negligible quantity.

In the present study the resistance to movement of the lungs was evaluated in sixteen patients with heart disease. These patients are the same individuals described in Part I, with two exceptions. The patients were breathing air during these studies. Pressure-flow diagrams were obtained by plotting $P_T - P_L$ against flow. In Figure 4 the mean pressure-flow diagram for the group of patients with cardiac disease is compared with the mean pressure-flow diagram for a group of normal subjects.[7] It is evident that a greater pressure is required to produce a given level of flow in the group of patients with heart disease than in the normal subjects. However, there was considerable overlapping between the individual curves obtained on the two groups.

A mathematical equation describing these pressure-flow relationships has been published.[7] In essence this equation, a polynomial, consists of three terms: The first term is the linear term which represents the laminar flow portion of the gas flow resistance. The second term is the quadratic term which represents the turbulent flow portion of the gas flow resistance. The third term represents tissue friction. The linear and quadratic coefficients were calculated from the pressure-flow diagrams of the patients with heart disease and are given in Table III. The mean linear coefficient in these sixteen patients was 2.63 (SD ± 1.43). This figure is significantly higher ($p = .02$) than the mean linear coefficient for normal subjects, 1.50 (SD ± 0.47). This increase in the linear coefficient is not of the same magnitude as that encountered in patients with pulmonary emphysema in which the mean linear coefficient for patients was 6.04. The same findings applied to the quadratic coefficients. The mean quadratic coefficient for patients with heart disease was 1.02 compared with 0.71 for normal subjects and 1.87 for patients with pulmonary emphysema. A glance at the individual figures in Table I for the linear and quadratic coefficients for patients with heart disease shows that not all patients had increased resistance to breathing. Those patients with increased resistance had severe heart disease and had had several bouts of congestive failure. However, not all patients with severe heart disease showed increased resistance. No correlation was found between the resistance to breathing (linear coefficient) and the reduction of vital capacity. (Fig. 5.)

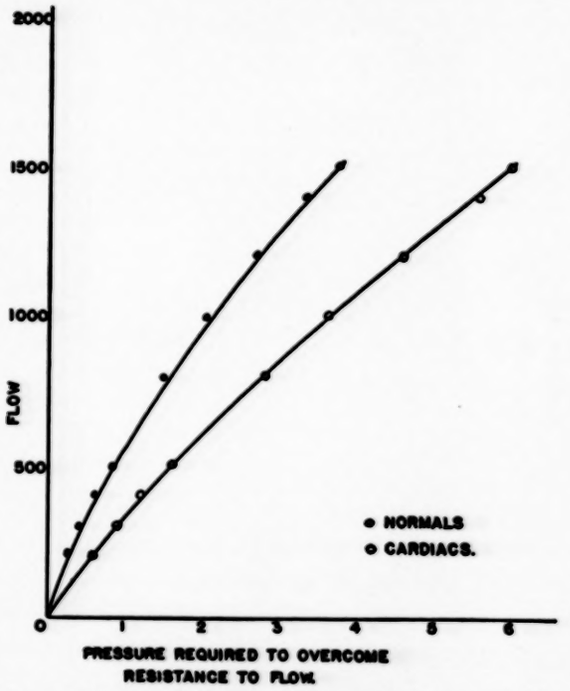

FIG. 4. The mean pressure-flow curves for normal subjects and for patients with heart disease, both breathing air. Flow is in cc. per second and resistance is in cm. H_2O.

It was considered desirable to determine whether this increased resistance to breathing

in certain patients with heart disease was due to increased tissue friction or to increased resistance to gas flow. This was done by having seven of the sixteen patients with heart disease breathe two gases with different physical properties: air, and a mixture of 80 per cent argon and 20 per cent oxygen. Four of these seven patients showed markedly increased resistance to breathing. By means of the mathematical analysis referred to earlier, the ratios of the linear coefficients obtained while breathing air and while breathing argon-oxygen and the ratios of the quadratic coefficients for air and argon-oxygen were calculated. (Table III.) The mean ratio of the linear coefficients for these seven patients was 1.22 and the mean ratio of the quadratic coefficients was 1.41. These ratios closely approximate the ratios of the respective viscosities of the two gas mixtures, 1.18 in the case of the linear terms, and the ratio of the respective densities, 1.33 in the case of the quadratic terms. This indicates that tissue friction is a negligible quantity in the increased resistance to breathing in patients with heart disease.[7] Almost all the frictional resistance to breathing is caused by resistance to laminar and turbulent gas flow.

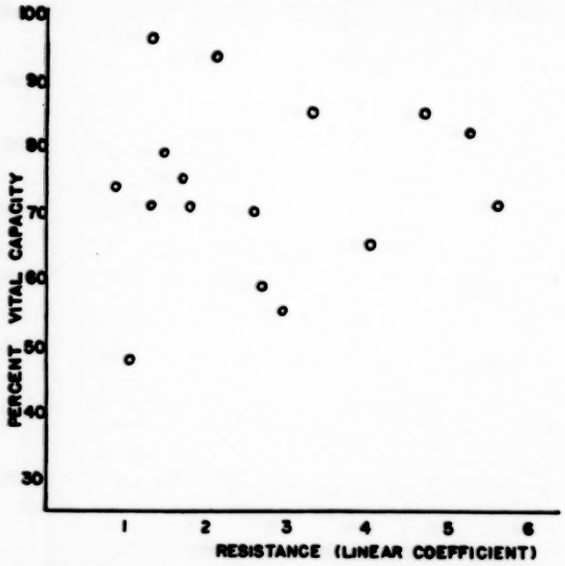

FIG. 5. Correlation of the resistance to breathing (linear coefficient) and the vital capacity (represented as per cent of the normal expected vital capacity) in patients with heart disease.

One possible cause of this increased resistance to gas flow is edema of the bronchial walls and fluid lining the bronchiolar lumens. Both of these factors would act to reduce the diameter of the bronchioles. Another possible explanation is that the bronchioles of some areas of the lungs of patients with heart disease are intermittently obstructed by fluid and therefore do not con-

TABLE III

STUDIES ON THE RESISTANCE TO BREATHING IN PATIENTS WITH HEART DISEASE

Case No.	Linear Coefficient for Air (N_1)	Linear Coefficient for Argon-Oxygen (A_1)	$\frac{A_1}{N_1}$	Quadratic Coefficient for Air (N_2)	Quadratic Coefficient for Argon-Oxygen (A_2)	$\frac{A_2}{N_2}$
1	0.82	1.01	1.23	1.20	1.60	1.33
2	3.26	3.98	1.22	0.95	1.12	1.18
3	2.51	2.95	1.17	0.90	1.45	1.61
4	1.37	1.61	1.17	0.87	1.17	1.35
5	1.03	1.29	1.28	0.73	1.01	1.38
6	4.64	5.53	1.19	1.53	2.21	1.44
7	4.01	5.21	1.30	1.72	2.73	1.57
8	5.52	....	....	0.87	....	....
9	1.63	....	....	0.67	....	....
10	2.67	....	....	0.84	....	....
11	2.96	....	....	1.08	....	....
12	5.21	....	....	2.19	....	....
13	1.42	....	....	0.82	....	....
14	2.08	....	....	0.96	....	....
15	1.71	....	....	0.35	....	....
16	1.28	....	....	0.69	....	....
Means	2.63 (SD ± 1.43)	3.08	1.22	1.02 (SD ± 0.43)	1.61	1.41
Means for normal subjects[7]	1.50 (SD ± 0.47)	1.87	1.25	0.71 (SD ± 0.26)	0.99	1.41

tribute to lung ventilation. In order to maintain adequate total ventilation the remaining functioning portions of these lungs would have to be overventilated. This would require higher levels of flow in the functioning parts of the lungs which in turn would require a higher pressure drop for a given level of respiratory flow.

It appears from this study that increased resistance to gas flow in the respiratory tree is a variable phenomenon in patients with heart disease. Certain patients with exertional dyspnea and a reduced vital capacity have no evidence of an increased resistance to gas flow. This is in contrast to patients with pulmonary emphysema in which all patients demonstrated an increased resistance.[7] It thus appears that exertional dyspnea in heart disease is more closely related to the reduction of vital capacity and associated alteration in the elastic properties of the lung than to resistance to gas flow in the bronchial tree.

Unfortunately, it was impossible to study many patients with orthopnea and marked evidence of pulmonary edema. One such case was studied (Case 8) and demonstrated a markedly increased resistance to gas flow. It seems likely that the most marked resistance to gas flow would be found in patients with pulmonary edema in which the bronchial tree is filled with fluid. It is interesting to speculate on the relationship of this increased resistance to gas flow to cardiac asthma. It was shown in a study of pulmonary emphysema[7] that when there is a marked increase in resistance to gas flow in the smaller bronchioles the intrathoracic pressure becomes positive during expiration. If the intrathoracic pressure exceeds the pressure within the unsupported bronchioles, the bronchiole tends to collapse. This in turn leads to a further increase in gas flow resistance. This mechanism could account for the asthmatic character of the paroxysms of dyspnea associated with pulmonary edema in heart disease.

SUMMARY

1. Using intraesophageal pressure as a measure of intrathoracic pressure, the elastic forces of the lung were studied in patients with heart disease. Pressure-volume diagrams were constructed by plotting the degree of lung inflation against the static intrathoracic pressure. An alteration in the elastic forces in the lungs of these patients was shown by the finding of an increase in the pressure required to produce a 100 cc. change in lung volume as compared with normal subjects.

2. A high correlation was demonstrated between the reciprocal of the vital capacity and the pressure change per 100 cc. change in lung volume both in normal subjects and patients with heart disease. The lung elasticity curves for normal subjects and patients with heart disease were identical when the level of lung inflation was expressed in terms of per cent of the vital capacity.

3. Pressure-flow curves were obtained from patients with heart disease. Comparison of the pressure-flow relationships obtained in these patients when breathing air and argon-oxygen demonstrated that tissue friction was a negligible factor and that the resistance to movement of the lungs was caused by resistance to gas flow.

4. Resistance to air flow was evaluated in patients with heart disease. It was found to be increased in certain patients with heart failure and normal in other patients. No correlation was found between resistance to air flow and reduction of vital capacity in these patients.

5. There may be no increase of resistance to air flow in patients with cardiac disease and exertional dyspnea. For this reason it appears that exertional dyspnea is most closely related to the reduction in vital capacity and altered elastic properties of the lung. On the other hand, it is likely that increased resistance to air flow plays an important role in the dyspnea of cardiac asthma.

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Respiratory Acidosis in Patients with Emphysema*

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Respiratory acidosis in patients with obstructive emphysema is a clinical entity which occurs with considerable frequency and in which diagnosis and treatment can be guided in large part by physiologic principles. Inadequate alveolar ventilation is the immediate cause of respiratory acidosis, and elevation of alveolar and arterial carbon dioxide tension (P_{CO_2}) is the specific indication that the condition exists. It is seldom associated with pulmonary disease which is circumscribed in its distribution, and it is seldom associated with generalized pulmonary disease if the airways remain patent. In patients with generalized obstructive emphysema, however, the superimposition of bronchitis, pneumonia or pulmonary congestion due to heart failure may lead to acute respiratory acidosis. Chronic respiratory acidosis may develop after a series of acute episodes.

This report deals with the physiologic mechanisms, clinical appearance and treatment of respiratory acidosis in eight emphysematous patients. Five demonstrate the acute form of the disease and three the chronic form.

Alveolar Hypoventilation. Total ventilation is the amount of gas exhaled per minute, and it is composed of a dead space component and an alveolar component. The dead space gas is so called because it fails to take part in gas exchange. That portion of the total ventilation which reaches the diffusing surface of the lung and which therefore takes part in gas exchange is called the alveolar ventilation. If there is an abnormally large proportion of dead space gas in the expired gas, alveolar ventilation may be low even though total ventilation is normal. Because of its close relationship to arterial P_{CO_2}, alveolar ventilation is more closely related to the problem of respiratory acidosis than is total ventilation.

Generalized obstruction of the airways is the most important cause of alveolar hypoventilation in the group of patients under consideration. The obstruction may result from intrinsic disease of the airways or from loss of elastic support for the smaller airways. Intrinsic disease may include bronchospasm, inflammation, fibrosis, secretions, edema or any combination of these factors which narrows the lumens of the airways.

Neergaard and Wirz,[1] Christie[2] and more recently Dayman[3] have investigated the relationship of lung elasticity to the patency of the smaller airways and to the resistance to airflow through such channels. During expiration, when gas flows from the alveoli out through the bronchioles, the pressure in the alveoli surrounding the bronchioles is greater than the intrabronchiolar pressure. This pressure gradient tends to collapse the bronchioles unless they are supported by the radial tension of the elastic fibers. In the presence of decreased lung elasticity there is an increase tendency for the smaller airways to collapse and slow expiratory airflow. The degree of obstruction to airflow is more severe during forceful expiration because the pressure gradient tending to collapse the small airways is increased.

Intrinsic disease of the airways and loss of elastic support of the bronchioles frequently occur together and accentuate the obstruction to airflow. Abnormalities of the airways themselves often may be affected favorably by therapy whereas obstruction related to decreased lung elasticity would appear to be irreversible.

Abnormalities of the chest cage and various neuromuscular and musculoskeletal disorders may also lead to alveolar hypoventilation. These

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conditions are of great importance but are beyond the scope of the present paper.

Respiratory Acidosis. Respiratory acidosis is the biochemical result of alveolar hypoventilation, and its presence is indicated by elevation of the P_{CO_2} of the arterial blood. The relationships are as follows: for any given level of CO_2 output, changes in alveolar ventilation cause inverse changes in alveolar P_{CO_2}; and arterial P_{CO_2} is virtually identical to alveolar P_{CO_2}. Accordingly, a decrease in alveolar ventilation is followed immediately by an increase in arterial P_{CO_2}.

The relationship between the P_{CO_2} and pH of the blood can be discussed in terms of the Henderson-Hasselbalch equation, which defines certain fundamental acid-base relationships in blood serum.

$$pHs = pK' + \log \frac{(HCO_3^-)}{(H_2CO_3)}$$

Since carbonic acid concentration is directly proportional to the partial pressure of CO_2, the expression can be re-written as follows (introducing numerical values for the constants):

$$pHs = 6.10 + \log \frac{(HCO_3^-)}{0.0301\ P_{CO_2}}$$

Changes in pH are seen to be dependent upon changes in the ratio $(HCO_3^-)/P_{CO_2}$. The denominator of this ratio is determined by alveolar ventilation in relation to CO_2 output, while the numerator, bicarbonate concentration, is controlled by extrapulmonary (predominantly renal) mechanisms. Only secondarily do changes in ventilation affect (HCO_3^-) or changes in electrolyte concentrations affect P_{CO_2}.

The Henderson-Hasselbalch equation applies only to blood serum and the relationships in whole blood are more complicated. In whole blood buffer base includes not only base bound by (HCO_3^-) but also base bound by other buffers, chief among which is hemoglobin. These buffers constitute additional extrapulmonary factors affecting the pH of whole blood and causing it to vary in a manner which is quantitatively a little different from serum. These relationships can be visualized in the nomogram of Singer and Hastings.[4]

We shall use the nomenclature of Singer and Hastings according to which elevation of whole blood buffer base is considered to be an indication of "metabolic" alkalosis, and an elevation of arterial P_{CO_2} an indication of "respiratory" acidosis.[4] When both factors are simultaneously deranged, the decision as to which is primary and which secondary is based on additional information regarding the sequence of events in the particular patient.

Changes in arterial P_{CO_2} follow changes in alveolar ventilation almost instantaneously while secondary changes in whole blood buffer base require days or weeks to reach completion. For this reason a patient with acute respiratory acidosis, in whom secondary metabolic changes have not yet occurred to an appreciable extent, can quickly regain a normal acid-base pattern if his depressed alveolar ventilation is restored to normal. If, however, the period of respiratory acidosis had been prolonged and a secondary increase in whole blood buffer base has occurred, the period required to restore a normal acid-base pattern must likewise be prolonged, even assuming that alveolar ventilation can be increased to a normal level.

The pulmonary abnormalities which lead to respiratory acidosis likewise cause a reduction in the oxygen saturation of the arterial blood, unless the concentration of oxygen in the inspired air is increased. Impairment of alveolar ventilation, of the distribution of gas and blood within the lungs, and of diffusion across the alveolar membrane may contribute to the depression of the oxygen saturation of the arterial blood. Reduction in alveolar ventilation increases the partial pressure gradient of oxygen between the outside air and the alveoli and this increased gradient is manifested by a reduction in alveolar P_{O_2}. Abnormal distribution of gas and blood within the lungs leads to a reduction in the oxygen saturation of the arterial blood because some blood passes through areas which are very poorly ventilated. The admixture of this poorly oxygenated blood lowers the oxygen saturation of the mixed arterial blood. If the patient's pulmonary disease is such as to cause severe impairment of diffusion across the alveolar membrane and if the general level of alveolar P_{O_2} is low, a significant P_{O_2} gradient may remain between the alveolar gas and the blood leaving the alveolar capillaries. Such a gradient also contributes to the lowering of arterial oxygen saturation. Because of the severity of the pulmonary disease which is ordinarily present in patients with respiratory acidosis, all these mechanisms are frequently operative and the resultant arterial oxygen saturation is often very low.

CLINICAL CHARACTERISTICS

Acute respiratory acidosis should be suspected in emphysematous patients in whom bronchopneumonia, severe bronchitis, asthma or acute heart failure has developed. Relative immobility of the chest, tachypnea, retraction of the intercostal spaces, marked diminution of breath sounds, inability to raise secretions and cyanosis are also indicators of the possible development of the syndrome. The administration of oxygen is accompanied by lessening of the cyanosis but by further reduction in ventilation and increasing drowsiness. The decrease in ventilation results from the elimination of the hypoxic stimulus to the respiratory mechanism. Drowsiness, which may progress to coma if oxygen therapy is prolonged, is related to the increasing severity of respiratory acidosis but the precise mechanism is not clear[6,16]

Emphysematous patients with chronic respiratory acidosis present many of the signs and symptoms just described but these signs and symptoms are of long-standing and are not related to a recent acute episode. Ordinarily the dyspnea is less severe than in the patient with acute respiratory acidosis although the inadequacy of alveolar ventilation, as indicated by the arterial P_{CO_2}, may be of equal degree. Because chronic cor pulmonale with right heart failure is frequently associated with chronic respiratory acidosis, the presence of the former increases the likelihood that the latter may be present. Polycythemia, if present, also suggests the possibility of chronic respiratory acidosis.

Materials and Methods. Serial studies of arterial blood were performed in five patients with acute respiratory acidosis and three with chronic carbon dioxide retention. The blood was analyzed immediately for carbon dioxide and oxygen tensions, according to the method of Riley, Proemmel and Franke.[7] The carbon dioxide content of the blood was measured according to the method of Van Slyke and Neill.[8] Hematocrit determinations were done in Wintrobe tubes. The pH of the serum and the whole blood buffer base were estimated from the nomogram of Singer and Hastings.[4] Gross spirometry and residual air determinations were done as described by Baldwin, Cournand and Richards.[9]

Results. The results of the arterial blood studies are shown in graphic form in Figures 1 to 9. Case histories are presented and are summarized under the appropriate graphs.

Comment. The relationships between arterial P_{CO_2} and whole blood buffer base follow a fairly consistent pattern. Elevation in P_{CO_2}, if promptly restored to normal by increase in alveolar ventilation, may cause little elevation in buffer base. (Fig. 4.) This quick return to normal acid-base relationships represents the ideal in the treatment of acute respiratory acidosis. If reduction in the elevated P_{CO_2} is more gradual, the buffer base may rise at first, as shown in Figure 5. Both P_{CO_2} and buffer base may then gradually return toward normal levels with pH remaining within normal limits during this period. (Fig. 5.) In an important group of patients with chronic respiratory acidosis both P_{CO_2} and buffer base remain permanently elevated and pH remains permanently lowered to a variable extent. (Figs. 6, 8 and 9.) In none of the patients studied did the arterial oxygen tension return to normal after treatment. In those cases in which the P_{CO_2} returned to normal the low arterial P_{O_2} can be attributed, not to inadequate alveolar ventilation of the lung as a whole, but to the passage of blood through isolated areas in which ventilation was poor or non-existent. When the P_{CO_2} remained high the additional factors mentioned contributed to the low arterial oxygen.

The arterial blood changes provide clues to mechanisms which may cause P_{CO_2} and buffer base to climb progressively in patients with chronic respiratory acidosis. All in the group of patients with whom we were concerned had severe emphysema with chronic airway obstruction and a chronic increase in the work of breathing. It is generally recognized, and our studies provide further evidence, that the superimposition of pulmonary infection or heart failure in such cases may increase the work of breathing to the point at which inadequate ventilation and an acute elevation of P_{CO_2} occurs (acute respiratory acidosis). In Figure 7 it is shown that physical exercise may also cause an acute elevation of P_{CO_2}. From these bits of evidence it seems likely, as has been suggested by others,[5] that a succession of episodes may occur during which the P_{CO_2} is temporarily elevated. If an associated succession of small increments in buffer base should accompany these episodes, there would be an increasing tendency for P_{CO_2} to fail to return to its previous level, and the stage would be set for the development of chronic respiratory acidosis.

TREATMENT OF ACUTE RESPIRATORY ACIDOSIS

In acute respiratory acidosis due primarily to generalized airway obstruction the response to vigorous treatment is gratifying and in most cases the acid-base abnormality can be reversed within a few days.

1. *Bronchodilators.* Isuprel® 1:200 was given by aerosol inhalation to all the patients in this series. The nebulizer was operated either with the hand bulb or with oxygen under pressure. When the patient was comatose the nebulizer was sometimes fastened to the pillow and directed toward the patient's face, or the aerosol was introduced into the oxygen tent. Both of these procedures proved wasteful and less effective than spraying the aerosol directly into the patient's mouth with the nose pinched shut. Patients who were able to cooperate were asked to exhale maximally before inhaling the aerosol. In this way the bronchodilator was carried deep into the bronchial tree. Severely obstructed patients were given nebulized bronchodilator for five minutes of each hour until breathing became easier. Overdosage on this regimen did not occur, perhaps because the inadequate ventilation permitted only a small proportion of the drug to reach the alveoli. If a significant increase in pulse rate should occur, aerosol therapy should be interrupted temporarily. Isuprel was used freely in the presence of heart failure if indicated because of airway obstruction. No serious toxic manifestations were observed. No other aerosols were used although several other products are believed to be equally effective. Our success in opening the airways, facilitating the raising of secretions, reducing the work of breathing and increasing ventilation in actue respiratory acidosis is thought to have resulted primarily from unusually intensive, repeated and prolonged use of bronchodilator.

Aminophylline was also administered freely by vein and by rectum. Intravenous medication may be extremely helpful in starting treatment in the occasional patient whose airways are so obstructed that inhaled bronchodilator cannot reach the bronchioles in appreciable quantity.

2. *Antibiotics.* Adequate antibiotic administration is of great importance in the treatment of these patients since inflammatory swelling of the bronchiolar mucosa contributes to the obstructive process. A variety of agents was used in the cases reported (penicillin, gantrisin,® chloromycetin,® aureomycin®). The combined effects of antibiotic and bronchodilator were clinically manifested by increased sputum, lessening cyanosis, auscultatory evidence of increased ventilation, and decreased lethargy and confusion.

3. *Oxygen.* The hazards of oxygen therapy in patients unable to produce adequate alveolar ventilation have been emphasized by Hickam et al.[6] and others. Unless ventilation can be sustained by the simultaneous use of a mechanical respirator, prolonged oxygen therapy should be avoided, both because the patient may become comatose and because the associated increase in arterial P_{CO_2} leads to a secondray rise in buffer base; this in turn further reduces the level of ventilation to which the patient will return when removed from oxygen. The patient who has been overtreated with oxygen may become so hypoxic when out of oxygen that it is impossible to remove him from the oxygen tent. This difficult situation can be avoided by using oxygen sparingly, as discussed subsequently.

The hazards of oxygen therapy do not alter the important rule that oxygen should be given when the degree of hypoxia is very severe. The deleterious effects of hypoxia must be balanced against the deleterious effects of the increased respiratory acidosis which accompanies oxygen therapy in these patients. In order to balance these factors it is necessary to have approximate knowledge of the arterial oxygen saturation and P_{CO_2}, yet neither of these values can be gauged with sufficient accuracy on clinical grounds alone. The decision regarding oxygen therapy is therefore greatly facilitated by laboratory analysis of the arterial blood. The following working principles are suggested in administering oxygen to patients with acute respiratory acidosis: (1) give oxygen only if the arterial oxygen saturation is below 85 per cent; (2) provide only a moderate increase in the oxygen concentration of the inspired air (40 per cent is adequate and will depress ventilation less than 100 per cent oxygen); (3) give oxygen intermittently by removing the patient from the high oxygen atmosphere each hour for as long a period as can be tolerated; (4) give vigorous bronchodilator therapy in association with oxygen therapy. In this way we have been able occasionally to prevent any rise in arterial P_{CO_2} during oxygen therapy and have thus derived the benefit of increased oxygenation without an associated increase in respiratory acidosis.

The working principles for administering oxygen can be modified if oxygen is delivered

through an intermittent positive pressure regulator and face mask. Under these circumstances it may be possible to administer 100 per cent oxygen without the decrease in ventilation which would otherwise occur. Bronchodilator can be given at the same time by spraying the aerosol into the stream of inspired oxygen.

4. *Treatment of Heart Failure.* The presence of heart failure and pulmonary congestion increases the work of breathing and decreases the amount of work which the patient is able to perform. Pulmonary congestion decreases the vital capacity and alters the visco-elastic properties of the lungs. Furthermore, the presence of edema fluid leads to obstruction of the smaller airways and permits blood to pass through poorly ventilated areas, causing a decrease in the arterial oxygen saturation.

Harvey et al. have discussed the treatment of cardiopulmonary failure at length.[10] Digitalis, diuretics and antibiotic drugs have been shown to be effective in dealing with this complicated process. Phlebotomy is indicated in the presence of polycythemia.

5. *Mechanical Respirators.* The use of mechanical respirators may pose various problems. Patients with acute respiratory acidosis may be unable to lie flat in a body respirator and it may be difficult to gain their cooperation when intermittent positive pressure is applied at the mouth. In severely obstructed patients who are unable to cooperate, ventilation may actually decrease when such measures are attempted. Furthermore, reliance on respirator therapy may divert the attention of the medical and nursing staff from the other simple and effective measures which have been outlined. Nevertheless, when the intermittent positive pressure apparatus is skillfully managed it provides a means of administering oxygen without diminution in ventilation, and it also provides a convenient and effective means of administering nebulized bronchodilator.[11] An additional advantage, which applies particularly to certain special types of apparatus, is the aid provided in raising sticky secretions and thereby relieving airway obstruction.[17,18]

6. *Cortisone and Corticotropin.* These hormones may be effective in the patient with obstructed airways, as illustrated by Case III. It is ordinarily undesirable to use cortisone or ACTH in patients with infection and heart failure.

7. *Detergents.* When nebulized into the bronchial tree, detergents such as alevaire® may be effective in liquifying sticky secretions and making them easier for the patient to raise. Airway obstruction may thereby be diminished.

8. *Helium and Oxygen.* A gas mixture containing 80 per cent helium and 20 per cent oxygen will pass through narrowed airways more easily than room air or oxygen. Helium and oxygen may therefore be indicated on occasion to improve ventilation in severely obstructed patients. Since the concentration of oxygen in such a mixture is no higher than in room air, helium and oxygen does not provide a substitute for oxygen therapy in patients who are severely hypoxic.

TREATMENT OF CHRONIC RESPIRATORY ACIDOSIS

Several factors combine to make the treatment of chronic respiratory acidosis particularly difficult. The elevation in whole blood buffer base tends to restore the pH toward normal and reduces the stimulus to the respiratory center which results from a low pH. Furthermore, since successive increments in P_{CO_2} exert decreasing effects upon pH, there is decreasing sensitivity of the respiratory center to change in P_{CO_2}. In addition, the chronic severe hypoxia which usually accompanies chronic respiratory acidosis appears to dull the sensitivity of the control mechanisms. For all of these reasons it is difficult to restore the alveolar ventilation of such patients to normal, and it can be seen from Figures 6, 7 and 9 that our efforts to do so have not been successful.

It is not immediately obvious what the optimal level of alveolar ventilation is for patients in whom the work of breathing is greatly increased. From the point of view of homeostasis the P_{CO_2} should be maintained at 40 mm. Hg, but from the point of view of minimal over-all disability a somewhat higher value might conceivably be better. For example, in the patient who expends most of his available energy on breathing, it is reasonable to consider the possibility that more energy might be left over for other activities if the volume of ventilation were reduced, provided the deleterious effects of underventilation were not extreme. If this sort of compromise could be maintained within reasonable bounds, it might have something to be said for it, but the clinical evidence indicates that the milder degrees of chronic respiratory acidosis almost invariably progress to more severe degrees in which the patient's over-all disability is extreme. We therefore believe that efforts to reduce the

work of breathing should be directed, not toward reducing the minute volume of ventilation, but toward increasing the ease with which ventilation can be accomplished.

All of the specific forms of therapy discussed in connection with acute respiratory acidosis have a place in the treatment of the chronic form of the disease. However, oxygen therapy, if used at all, must be handled with even greater caution to avoid further depression of ventilation and permanent dependence upon oxygen. The following additional measures deserve mention.

1. *Pneumoperitoneum.* Cases 6, 7 and 8 were treated with pneumoperitoneum. The rationale for a treatment which restores the diaphragm to a more normal position seems reasonable, and temporary improvement is often reported. We have not been favorably impressed by the long term results, however, and the acid-base data in Figures 6, 8 and 9 give little indication that pneumoperitoneum delayed the gradual increase in arterial P_{CO_2}.

2. *Breathing Exercises.* The physiotherapeutic approach has recently been emphasized by Miller[12] and Allan.[13] There is no doubt that breathing exercises, properly performed, frequently result in subjective improvement and increased exercise tolerance. The patient usually appears more relaxed and ventilation is performed more efficiently. Significant lowering of a chronically elevated P_{CO_2} has not to our knowledge been observed.

3. *Mechanical Respirators.* In chronic respiratory acidosis the rationale for attempting to increase ventilation by the use of body respirators or intermittent positive pressure breathing is impressive. Depression of the stimulus to breathe constitutes an important part of the syndrome, and prolonged increase in ventilation by mechanical means, with reduction in P_{CO_2} and whole blood buffer base, may bring about an increase in the involuntary breathing stimulus. Ventilation must be assisted virtually continuously for several days in order to give time for reduction in buffer base. When this is done good results have been reported[14] but the undertaking is so difficult and so expensive in time, equipment and skilled personnel that it is impossible of accomplishment under most circumstances.

Short periods of treatment with intermittent positive pressure apparatus have been tried extensively in chronic obstructive disease.[11] By making possible the simultaneous administration of nebulized bronchodilator and oxygen, without diminution in ventilation, the mechanical respirator fills an important therapeutic need.

4. *Carbon Anhydrase Inhibitor.* There have been favorable reports concerning the effectiveness of the carbonic anhydrase inhibitor, diamox,® in respiratory acidosis.[15] In our hands the drug has been most useful in patients with chronic respiratory acidosis and heart failure.* Its respiratory effect is thought to be secondary to the diuretic effect. Ventilation is thought to be facilitated by the reduction in pulmonary vascular congestion and edema, and stimulated by the reduction in the pH of the arterial blood.

5. *Minimal Use of Drugs Which Depress the Respiratory Centers.* Narcotics and sedatives of all sorts should be administered with the greatest care, if at all, to patients with respiratory acidosis because of the likelihood that further depression of ventilation will occur. These patients are very susceptible to the respiratory depressant effects of such drugs. We have seen a patient whose arterial P_{CO_2} rose to 87 mm. Hg when, by mistake, three tablespoonfuls of chloral hydrate were taken during the course of one sleepless night. Following treatment her P_{CO_2} returned to 55 mm. Hg, a level which probably represented approximately her previous state.

The dilemma in the treatment of respiratory acidosis may be summarized as follows. The patient suffers from hypoxia and hypercapnia, yet treatment of the former with conventional oxygen therapy increases the severity of the latter. Mechanical respirators, when operating properly, offer the combined advantages of oxygen therapy and increased ventilation, and therefore provide a direct approach to the twin evils of hypoxia and hypercapnia. On the other hand, the experience described in this paper demonstrates that acute respiratory acidosis can often be treated successfully without using mechanical respirators. This experience is thought to have some practical value since only measures which are generally available were applied. Furthermore, the principles which make possible a judicious choice between undesirable physiologic alternatives have general applicability. It is our hope that the discussion of treatment, which is by no means an exhaustive survey of the many therapeutic aids available, will be viewed in this light.

* Diamox supplied through the courtesy of the Lederle Laboratories Division, American Cyanamide, New York, N. Y.

CASE REPORTS

Acute Carbon Dioxide Retention

CASE I. (M. P., Johns Hopkins Hospital Hist. No. 215347). A sixty-four year old Italian carpenter was admitted to the hospital on January 20, 1951, because of fever, cough and dyspnea increasing in severity for four days. A chronic cough had been present for many years, productive of large amounts of green, foul-tasting sputum, especially copious in the morning on rising. A 20 pound weight loss had occurred in the two years preceding admission.

Physical examination showed that the temperature was 99.4°F., the pulse 80, respirations 32 and blood pressure 160/100. The patient was producing copious amounts of greenish sputum and was severely dyspneic, cyanotic and orthopneic. The chest was held in the full inspiratory position and there was increase in the anteroposterior diameter. The diaphragm moved poorly, breath sounds were distant and there were coarse moist rales heard at the bases of the lungs. The liver edge could not be felt, and there was no ankle edema. The leukocyte count was 22.7 thousand, and the hematocrit 52 mm. The venous pressure was 160 mm. of saline solution, and the arm to tongue circulation time was 34 seconds (decholin®). The chest roentgenogram on January 20, 1951, showed some infiltration in the right upper lung field with increased bronchovascular markings. An electrocardiogram taken on January 22, 1951, showed high P waves. Routine culture of the sputum showed mixed flora, with pneumococci. Repeated studies of the sputum for acid-fast bacilli were negative. The initial treatment consisted of intermittent oxygen therapy in conjunction with frequently repeated inhalations of nebulized bronchodilator (isuprel, 1:200, aerosol). Penicillin was given intramuscularly in large doses and during the third week 4.0 gm. of gantrisin daily were added. On this regimen the patient rapidly became afebrile with improvement in dyspnea and decrease in the amount of sputum.

Comment: This patient came to the hospital with acute bronchopneumonia superimposed on chronic emphysema. There was extreme elevation of the arterial CO_2 tension (Pa_{CO_2}) without comparable elevation in the whole blood buffer base $(Bb)_b^+$, producing a lowered pH. (Fig. 1.) The values returned to the normal range during treatment with intermittent oxygen, penicillin and aerosol isuprel. The ratio of his residual volume to total lung volume on February 7, 1951, was 46 per cent, compatible with pulmonary emphysema. Presumably relief of inflammatory and spastic narrowing of the airways was largely responsible for reducing the

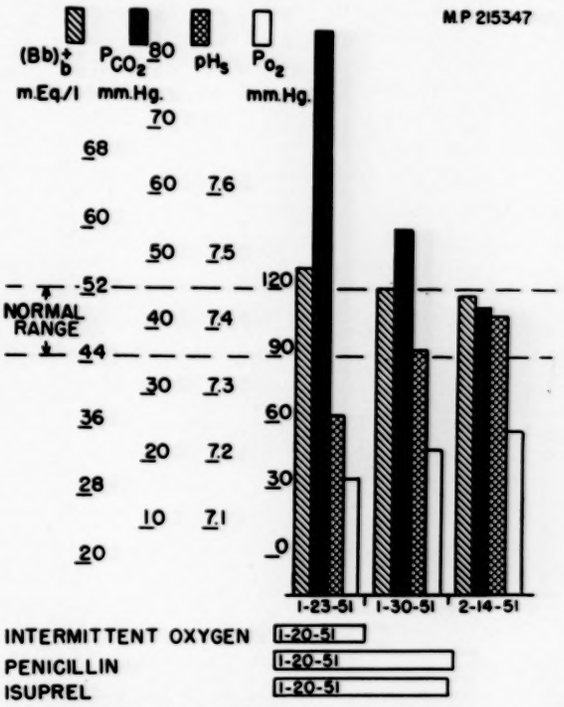

FIG. 1. Findings in Case I, showing an excellent response of the respiratory acidosis to bronchodilator and antibiotic therapy in a patient having an acute bronchopneumonia superimposed on moderately severe emphysema.

work of breathing and permitting a return to normal levels of alveolar ventilation.

CASE II. (Wm. Ba., Johns Hopkins Hospital Hist. No. 596591). A fifty-eight year old white male came to the hospital on February 2, 1952, complaining of shortness of breath and swelling of the abdomen of about one week's duration. He had been "gased" in World War I. Asthma with a chronic cough productive of moderate amounts of greyish sputum had been presented for thirty years. Two years prior to admission a vital capacity of 39 per cent of normal was recorded. For the six months preceding admission he had noted progressive dyspnea and orthopnea, associated with anorexia and weakness. Digitalization failed to relieve the dyspnea. There was a gradual increase in cough, sputum production, swelling of abdomen and ankles, and a progressive diminution of exercise tolerance.

Examination on admission showed the temperature to be 98°F., the pulse 100, the respiration 40 and blood pressure 115/80. The patient was cyanotic, dyspneic, plethoric and had marked tachypnea with very shallow breathing. There was very thick mucus in the throat and cardiogram showed right axis deviation, low amplitude of QRS, delayed precordial transition and abnormal P and T waves.

The patient was placed in an oxygen tent and treated with a low salt diet, digitoxin and aminophylline suppositories. The day after admission

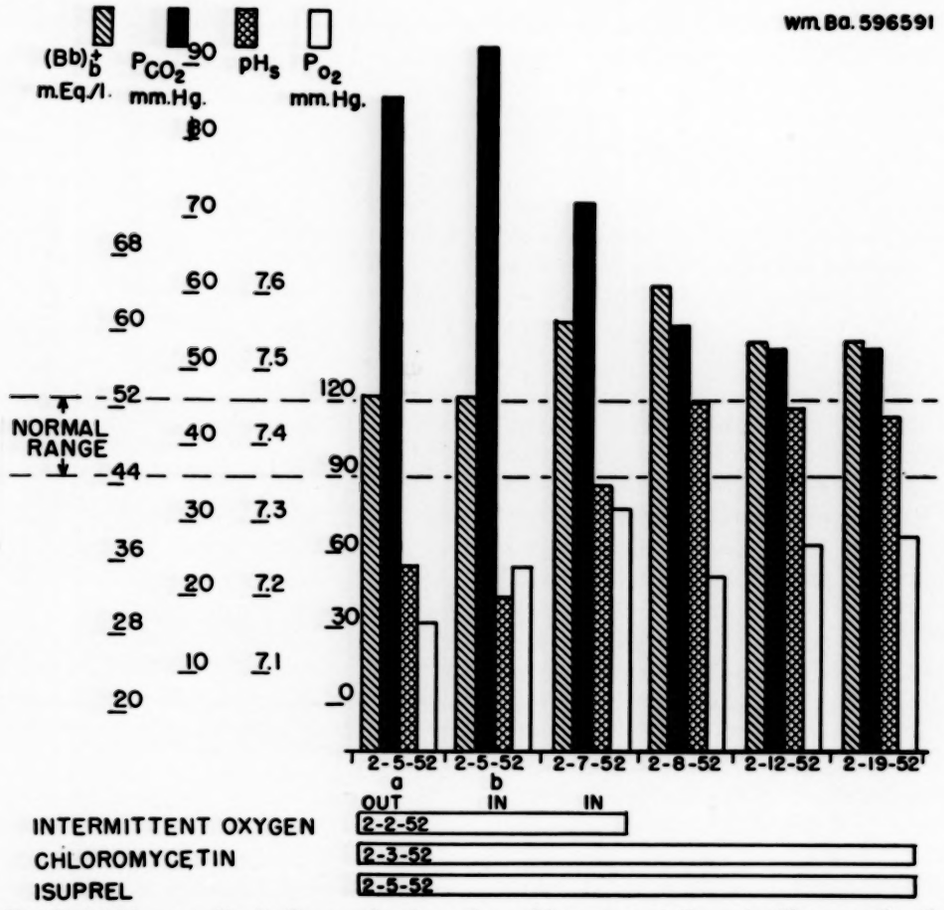

FIG. 2. Acid-base studies in Case II, showing a favorable response to bronchodilators and antibiotics in a patient having an acute pulmonary infection associated with emphysema and cor pulmonale. The first study (*a*) was performed with the patient out of the oxygen tent, and the second study (*b*) after thirty minutes in the oxygen tent. The rise in P_{CO_2} and fall in pH are notable.

paroxysms of cough produced very little sputum. The chest contour was emphysematous; the intercostal spaces retracted with inspiration and the breath sounds were very faint. Numerous wheezes and rales, inspiratory and expiratory, were heard throughout both lung fields. Ascites and hepatomegaly were present. There was slight ankle and presacral edema. The heart sounds were obscured by respiratory noises.

The venous pressure was 280 mm. of saline solution. The circulation time was twenty-four seconds (decholin). The hematocrit was 54 mm.; leukocytes numbered 10.5 thousand. An electrohe became unresponsive with a respiratory rate of 56 per minute. The lungs were filled with coarse rales and harsh inspiratory and expiratory wheezes were heard. A 500 cc. phlebotomy was performed. Thiomerin,® intravenous aminophylline and chloromycetin were administered. In addition, the patient was kept out of the oxygen tent during alternate one-half-hour intervals.

On February 5, 1952, the respiratory rate was 60 per minute. Initial blood gas studies showed extreme respiratory acidosis. (Fig. 2*a*.) Further elevation of arterial carbon dioxide tension and

lowering of pH were observed after thirty minutes in an oxygen tent. (Fig. 2*b*.) At this time 1 cc. of nebulized isuprel, 1:200, was blown into the oxygen tent every thirty minutes, and alternation every half hour between room air and a high oxygen atmosphere was begun. This regimen was continued for five days. There was gradual steady improvement. Sputum production increased considerably and a diuresis occurred. Oxygen was discontinued on February 9th. Aerosol isuprel was administered four times daily thereafter. On February 15, 1952, the patient was ambulatory. Examination of the lungs revealed good excursion of the chest and no rales or wheezes were heard. Serial electrocardiograms, interpreted as compatible with acute cor pulmonale, reverted to normal after clinical improvement.

Comment: This patient had an acute pulmonary infection with cor pulmonale superimposed upon chronic emphysema. Figure 2 shows the changes in the acid-base balance with therapy. Initially the patient had been given continuous oxygen therapy which increased the oxygen saturation of the arterial blood but also diminished the stimulus for breathing. For this reason the patient was allowed in the oxygen tent for one-half-hour intervals only, so that ventilation would not be suppressed over long periods of time. Therapy directed toward bronchodilatation and relief of pulmonary congestion and infection reduced the work of breathing and facilitated the return to a near normal rate of alveolar ventilation.

Case III. (Wm. Bo., Johns Hopkins Hospital Hist. No. 596796): A fifty-eight year old white male was admitted on February 19, 1952, because of severe dyspnea of approximately eighteen hours' duration. He was known to have chronic lymphatic leukemia, asthma and emphysema. He had received 10 mg. of nitrogen mustard two weeks before admission. On February 18, 1952, there was the sudden onset of severe dyspnea.

Examination on admission revealed a temperature of 99.4°F., a pulse rate of 100, respirations 40 and blood pressure of 130/80. He was in acute respiratory distress and quite cyanotic. The chest was increased in anteroposterior diameter. Coarse rhonchi were heard especially during the relatively long expiratory phase of breathing. Marked hepatosplenomegaly was present.

The patient was placed in an oxygen tent, given aminophylline intravenously, and isuprel (1:200) was sprayed into the tent. Eight hours later, after apparent improvement, he suddenly became drowsy, extremely cyanotic and stopped breathing. He was removed from the tent immediately and given artificial respiration and

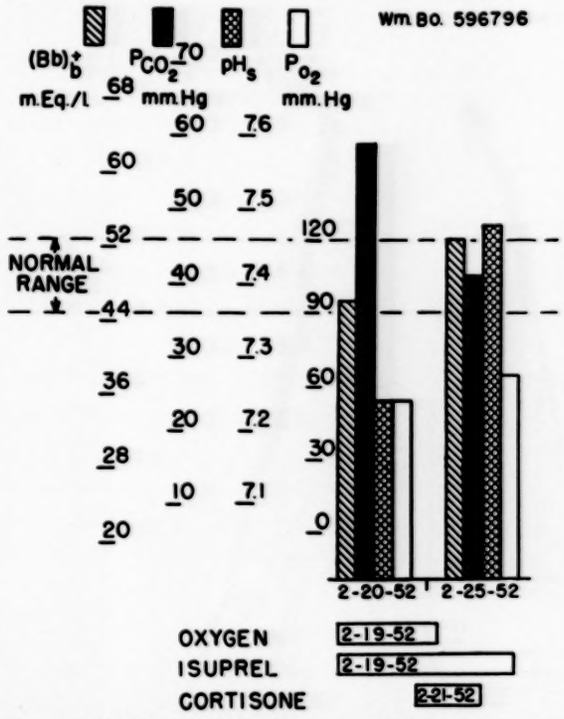

Fig. 3. Acid-base studies in Case III, a patient with severe emphysema and marked bronchial obstruction without much pulmonary infection. Clinically, it was believed that cortisone was helpful in relieving the bronchial obstruction.

intravenous aminophylline with return of consciousness. His condition remained essentially unchanged but he became extremely apprehensive when removed from the oxygen tent. On February 21, 1952, cortisone (50 mg. orally, every six hours) was started in the hope that it would relieve the airway obstruction. A few hours after the first dose of cortisone the patient coughed up some mucous plugs. A normal respiratory pattern followed almost immediately. By February 23rd oxygen was no longer needed. The patient was discharged on March 5, 1952.

Comment: This patient with severe emphysema developed signs of sudden obstruction of the bronchi, possibly due to infection and viscous secretions. This produced acute respiratory acidosis which was relieved by removal of obstruction of the bronchial tree. (Fig. 3.) The use of cortisone in this patient seems to have

been helpful, after antibiotics and other bronchodilators had produced little benefit. An oxygen tent had to be used continuously in this man (except when blood samples were drawn) because efforts to remove him from it resulted in severe apprehension.

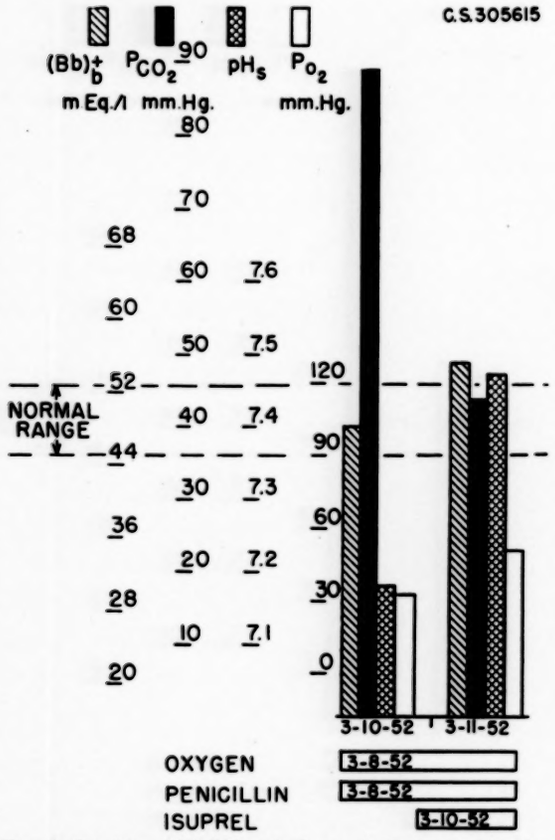

FIG. 4. Studies of acid-base balance in Case IV, showing a quick return toward normal values in an elderly patient with emphysema and bronchopneumonia.

CASE IV. (C. S., Johns Hopkins Hospital Hist. No. 305615). This seventy-five year old white man was admitted to the hospital on March 8, 1952, because of increasing lethargy of four days' duration. Asthma and a chronic cough were known to have existed for twenty years. Progressive exertional dyspnea had first been noticed in 1949. Four days prior to admission he caught cold and had increase in his non-productive cough. Dyspnea and mental dullness increased to the time of admission.

On examination the temperature was 100.4°F., pulse rate 110, respirations 40 per minute and blood pressure 110/60. Slight cyanosis was present. The chest was increased in anteroposterior diameter, and there was very little thoracic motion with respiration. The percussion note was hyperresonant. Fine rales were heard at the end of inspiration on auscultation, and wheezing with coarse squeaks occurred during the prolonged expiratory phase. The heart was not enlarged to percussion. The second pulmonic sound was louder than the second aortic sound. No murmurs were heard. The liver edge was percussed 2 cm. below the right costal margin. No ankle edema or presacral edema was noted.

The hematocrit was 43 mm., the leukocyte count was 14 thousand. An electrocardiogram showed a sinus tachycardia with high P waves in leads 2 and 3. X-ray of the chest revealed low, flattened diaphragms, and an increase of bronchovascular markings throughout both lung fields.

The patient was placed in an oxygen tent and given penicillin and intravenous aminophylline. After several hours his lethargy increased and respirations became extremely shallow and rapid. At this time the patient was temporarily removed from the oxygen tent and the first arterial blood studies were made. Severe oxyhemoglobin unsaturation and an increase in carbon dioxide tension were detected. (Fig. 4.) The penicillin dosage was increased and nebulized isuprel (1 cc. of 1:200 solution) was introduced directly into the patient's mouth every hour. The patient's nose was pinched off during the latter procedure to insure that the aerosol was inhaled. The patient was brought out of the oxygen tent one-half hour of each two-hour period. Six hours later considerable improvement in sensorium and depth of respiration was apparent. Sputum production had increased and breath sounds and coarse rales became audible in the chest. The second set of blood studies was performed approximately eighteen hours after initiation of this therapeutic regimen. The sensorium was quite clear and ventilation markedly improved. Although he appeared to be improving, the patient was found dead in bed early on the morning of the fourth hospital day.

Comment: This patient had profound, acute respiratory acidosis and improved remarkably in response to vigorous treatment. Complete reversion of a critically altered acid-base balance occurred within eighteen hours. The patient's sudden death could not be accounted for since an autopsy was not performed.

CASE V. (N. M., Johns Hopkins Hospital Hist. No. 433147). A sixty-one year old white male farmer was admitted to the hospital on February 25, 1953, complaining of severe

respiratory distress for three days. The patient had "double pneumonia" at forty years of age. Around 1937 episodes of shortness of breath and wheezing respirations occurred each spring and fall. The shortness of breath had become progressively more severe during the several months before admission. There was associated cough and purulent sputum. Two days prior to admission the patient was seen in the Accident Room in severe respiratory distress, thought to be asthma and pulmonary edema. He was given aminophylline and digitalis. He coughed up copious amounts of sputum and improved enough to return home. The following evening the patient again presented himself to the Accident Room with the same complaints and was admitted to the ward.

Physical examination revealed a critically ill, cyanotic, markedly dyspneic man with a temperature of 100°F., pulse 148 and respiratory rate of 36. The blood pressure was 120/70. Respirations were so labored that speech was limited.

The chest was very emphysematous and there were no visible respiratory excursions. Breath sounds were almost inaudible. Occasional wheezing was noted. The heart was enlarged to the left. Venous distention was prominent, and the liver was percussed 5 cm. below the right costal margin. The chest x-ray showed an infiltration of the right upper lung field. The arterial blood at this time showed extreme elevation of P_{CO_2}, with little secondary rise in buffer base. (Fig. 5.)

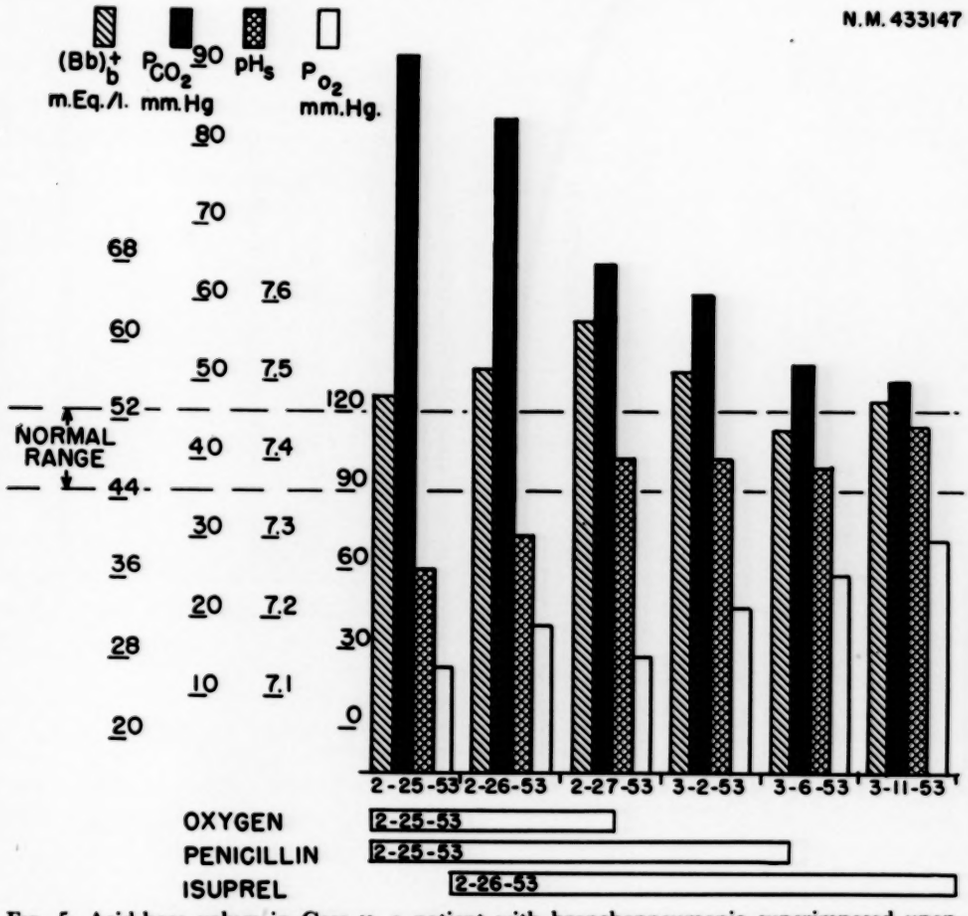

FIG. 5. Acid-base values in Case V, a patient with bronchopneumonia superimposed upon emphysema and cor pulmonale. There was gradual return toward normal in response to treatment with antibiotics and bronchodilators.

After initial treatment with aminophylline, penicillin, helium and oxygen by mask, phlebotomy and nebulized isuprel, the breath sounds improved and numerous wheezings and rales could be heard. The sputum became less viscous and increased in amount. At the same time the breath sounds became louder, as did the rhonchi

and wheeze. The degree of cyanosis lessened and the patient became more alert. By the ninth day of treatment he was considerably improved and able to be up in a chair. The chest x-ray showed radiolucent lung fields with no cardiac enlargement. The electrocardiogram was compatible with cor pulmonale.

Acute Carbon Dioxide Retention in Chronic Respiratory Insufficiency

Case VI. (E. W., Johns Hopkins Hospital Hist. No. 524348). This fifty-seven year old white female was admitted to the hospital for the third time on January 7, 1952, because of increasing dyspnea. Intermittent attacks of bronchial asthma had occurred during the previous thirty years. Exertional dyspnea was first noted seven years before admission and had gradually increased. The first hospitalization was in 1950 for severe shortness of breath. Pulmonary function studies showed advanced emphysema with arterial oxyhemoglobin unsaturation. Significant improvement occurred on a regimen including a low salt diet, digitalis, thiomerin, penicillin, aureomycin and respiratory exercises.

There was a second admission in 1951 for recurrence of dyspnea. In addition to measures previously used, pneumoperitoneum was started.

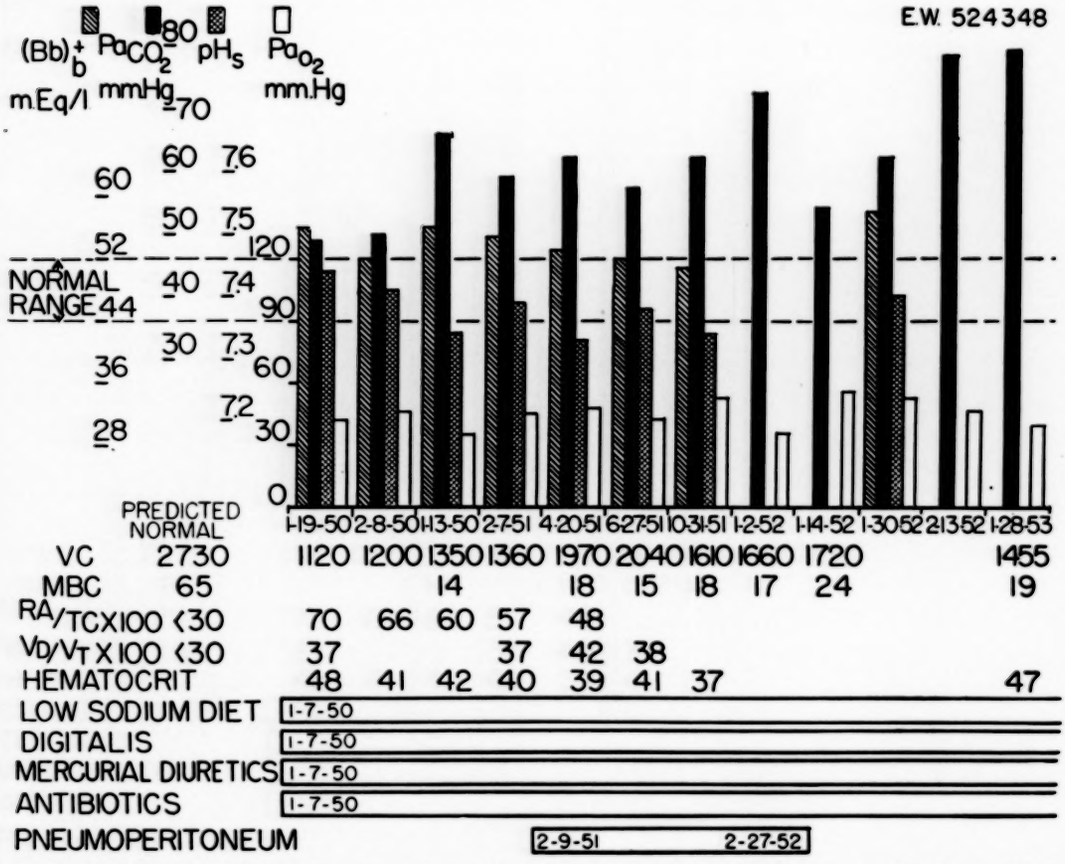

Fig. 6. Acid-base values in Case VI, a patient with emphysema and cor pulmonale, showing the gradual rise in P_{CO_2} despite all measures including pneumoperitoneum.

Examination on March 13, 1953, showed that the breath sounds were harsh over the anterior portion of the chest. There was some prolongation of the expiratory phase of respiration, and inspiratory post-tussic rales were heard at the left base.

Comment: This patient had cor pulmonale secondary to emphysema with a superimposed bronchopneumonia. Although the arterial P_{CO_2} decreased progressively during therapy, it was sufficiently high during the first three days to occasion a secondary rise in buffer base. After this, both P_{CO_2} and buffer base returned toward normal. (Fig. 5.)

Associated with this, improvement was noted. In November, 1951, the liver was palpated for the first time and there was roentgenographic evidence of cardiac enlargement. It was also found that the arterial carbon dioxide tension had begun to rise. After discharge from the hospital, in spite of bronchodilator drugs, a low salt diet, digitalis and mercuzanthin, dyspnea increased and ankle edema reappeared.

On the third admission in January, 1952, examination showed that the temperature was 99.8°F., the pulse 106, respirations 28 and blood pressure 120/80. The patient was severely dyspneic, orthopneic and cyanotic. The chest was barrel-shaped and the accessory muscles of respiration were in use. The thorax was hyperresonant to percussion. The breath sounds were distant, with an expiratory wheeze. Fine and medium rales were heard at the end of inspiration and the beginning of expiration. The heart was enlarged and the second pulmonic sound was louder than the second aortic sound. A pneumoperitoneum was present. The liver was felt 1 cm. below the right costal margin, and there was slight ankle edema. The electrocardiogram showed right axis deviation with delayed precordial transition and abnormal P waves compatible with cor pulmonale. The arterial P_{CO_2} was sharply elevated.

The patient improved remarkably with bed rest, intermittent thiomerin, ammonium chloride and aminophylline. The arterial P_{CO_2} decreased approximately 20 mm. Hg but was still abnormally high. (Fig. 6.) The patient was discharged taking digitalis, isuprel aerosol, intermittent ammonium chloride and aminophylline suppositories. The pneumoperitoneum was continued.

The patient remained cyanotic and dyspneic. On February 27, 1952, the pneumoperitoneum was discontinued without any noticeable objective or subjective change.

Comment: This patient showed improvement with the institution of pneumoperitoneum but the beneficial effects were not maintained. The decrease in arterial P_{CO_2} during the third hospital admission appeared to be related to reduction in pulmonary edema and congestive heart failure. A subsequent arterial blood study performed when the patient was ambulatory showed that the resting P_{CO_2} had again risen to a very high value. A further increase of 12 mm. Hg occurred when the patient exercised gently, but almost maximally, on the treadmill. (Fig. 7.)

Chronic Carbon Dioxide Retention

Case VII. (S. T., Johns Hopkins Hospital Hist. No. 1377110). A twenty-nine year old colored woman came to the hospital on September 8, 1950, complaining of shortness of breath of nine months' duration. She had undergone a

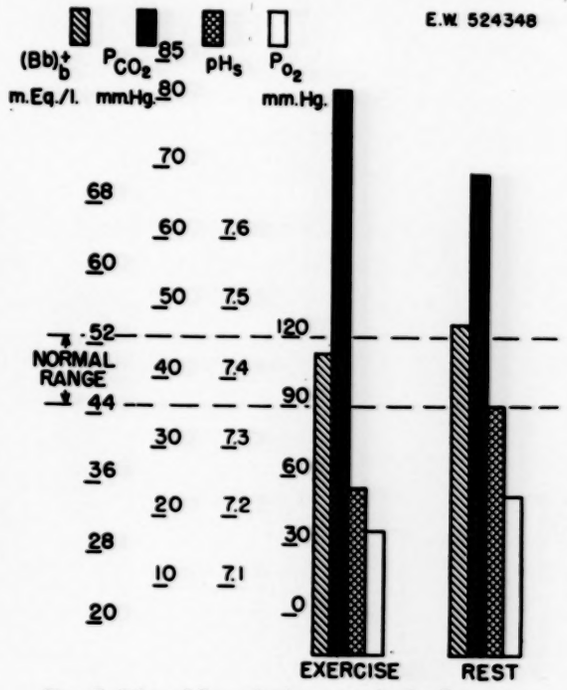

Fig. 7. Rise of P_{CO_2} during exercise in Case VI.

normal pregnancy eleven years prior to admission but in the second month of her last pregnancy, nine months before admission, there was the onset of ankle edema and increasing dyspnea. These symptoms did not improve after delivery in August, 1950, and she therefore came to the hospital. Examination showed a blood pressure of 130/90, an increase in the anteroposterior diameter of the chest, fine rales throughout both lung fields, poor descent of the diaphragm, and enlarged liver, ascites and ankle edema. The electrocardiogram showed right axis deviation. Cardiac catheterization at this time showed a cardiac index of 3.8 L. and a pulmonary arterial pressure at rest of 36/28. A diagnosis of cor pulmonale secondary to severe emphysema was made. The patient was digitalized, given bronchodilators, and a pneumoperitoneum was instituted on October 25th. Although there was no immediate improvement in the blood oxygen saturation or fall in carbon dioxide tension, the patient felt improved. The subjective improvement was not maintained with the continuation

of this therapy. The pneumoperitoneum was discontinued on April 13, 1951, without increase in symptoms. Because of increasing ankle edema she was readmitted to the hospital on July 25, 1951.

Examination showed that there was dyspnea, expiratory wheezes, fine rales over the lung fields, venous distention, hepatomegaly, ascites and ankle edema. On a regimen of salt restriction, digitalis, bronchodilators and bed rest, the dyspnea improved. The ascites and ankle edema regressed, and the liver was no longer palpable at discharge on August 21, 1951.

The patient was last seen in September, 1951. At that time there were again signs of respiratory and cardiac failure.

Comment: Although there was subjective improvement in the patient's condition with the start of the pneumoperitoneum, there was no objective evidence of improvement in lung volumes, oxygen saturation or carbon dioxide retention. (Fig. 8.)

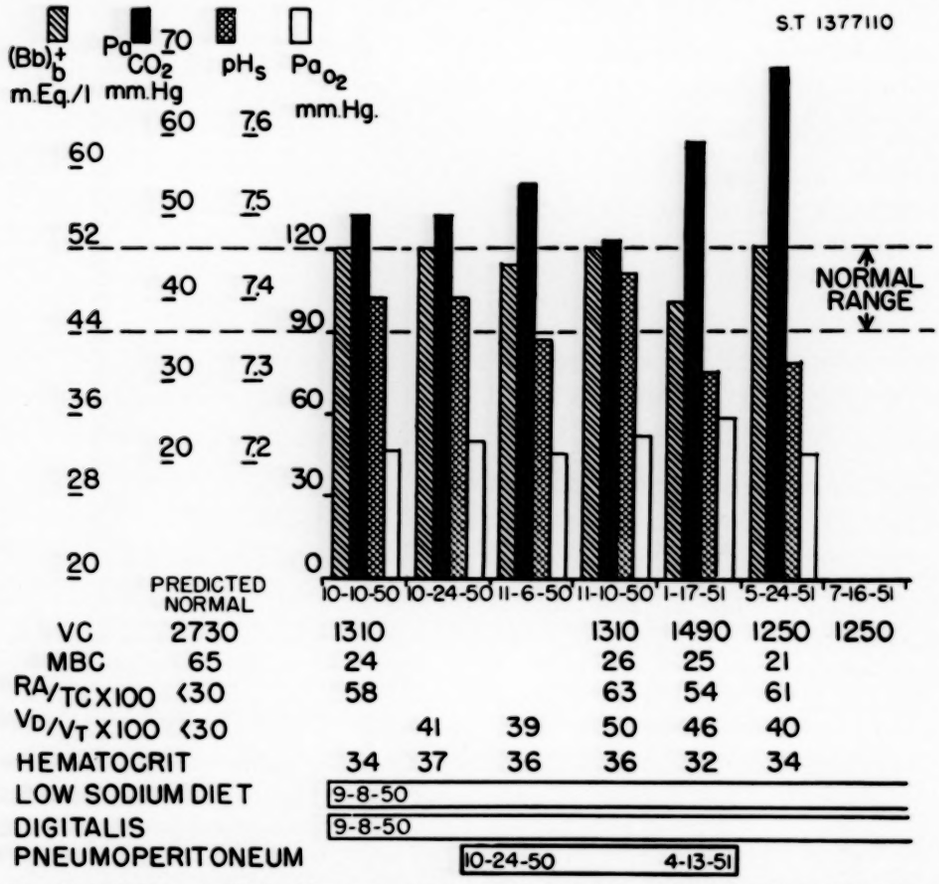

FIG. 8. Acid-base studies in Case VII, a patient with emphysema and cor pulmonale, showing the continued rise in P_{CO_2} despite therapy including pneumoperitoneum.

CASE VIII. (C. T., Johns Hopkins Hospital Hist. No. 486158). A sixty-seven year old colored man came to the Accident Room on January 14, 1949, acutely short of breath and was admitted to the hospital for the first time. For four years the patient had been treated at home for intermittent cardiac failure presumably on the basis of arteriosclerotic heart disease. For two months dyspnea had been worse, and the patient had restricted his activity and had been treated with a low salt diet and digitalis. In the Accident Room his temperature was 103°F., and blood pressure was 130/70. He was cyanotic, extremely short of breath; there were moist rales and wheezes over both lung fields, and there was moderate ankle edema. There was a productive cough but the patient was too weak to expectorate forceably. He was treated with 12 mg. of morphine, tourniquets, oxygen by mask, and 0.24 gm. of aminophylline intravenously. On this therapy there was slight improvement but after an hour he became confused and finally

comatose, and was admitted to the hospital. The breathing was Cheyne-Stokes in character with periods of apnea as long as forty-five seconds. The heart was believed to be greatly enlarged and there were frequent nodal extrasystoles.

On the ward he was treated initially with phase of breathing prolonged. The liver edge was felt 3 cm. below the costal margin in the right mid-clavicular line. There was moderate ankle edema. The chest roentgenogram showed an area of infiltration in the right upper lung field. The patient was thought to be suffering from

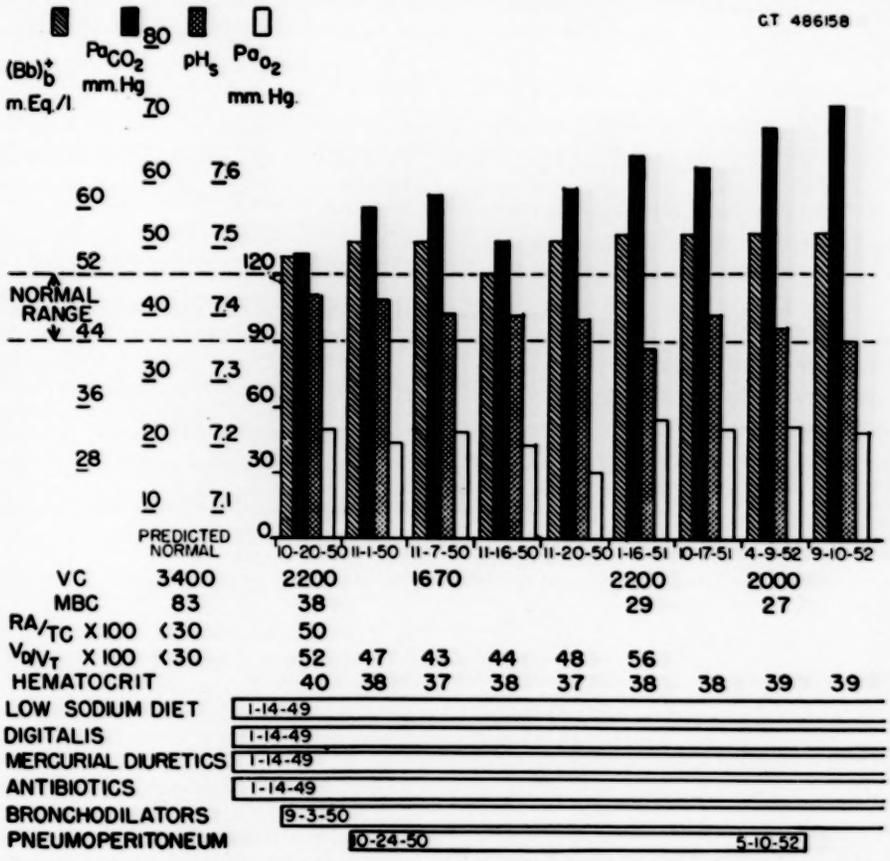

FIG. 9. Acid-base studies in Case VIII, a patient with emphysema and cor pulmonale, showing the gradual increase in P_{CO_2} despite pneumoperitoneum, antibiotics and bronchodilators.

caffeine and sodium benzoate and consciousness returned within a half hour. Penicillin was given because of the possibility of lobular pneumonia. Digitoxin, 0.2 mg. was given daily, and on a low salt diet he improved remarkably, being discharged on January 21, 1949, with a diagnosis of arteriosclerotic heart disease and failure.

He felt fairly comfortable at home on limited activity, bed rest and digitalis, until March, 1950, when he developed bloody sputum, fever and increasing ankle edema. On admission his temperature was 101°F., the pulse 98, respirations 48, and blood pressure 135/90. The patient was orthopneic and the chest emphysematous. There were moist rales at the lung bases, the breath sounds were distant and the expiratory

bronchopneumonia of the right upper lobe and was started on penicillin, oxygen, a low salt diet and digitoxin 0.2 mg. daily. On this therapy the temperature dropped to normal on the third day. The cardiac failure responded very slowly. On the sixth hospital day it was noted that the carbon dioxide combining power had risen markedly, and he was taken out of the oxygen tent. Thereafter, his cardiac failure slowly improved with the help of diuretics.

The patient felt well on limited activity at home but in September, 1950, the ankle edema and dyspnea increased and, despite diuretics, he had to be hospitalized on September 29, 1950. At this time he was dyspneic, cyanotic, breathing was shallow, there were moist rales at the lung

bases, breath sounds were distant, and the expiratory phase of respiration was prolonged. The heart was enlarged, there was a proto-diastolic gallop, the liver edge was felt 6 cm. below the costal margin and there was severe edema of the ankles and the sacral region. For the first time, right axis deviation was present with delayed precordial transition. The hematocrit was elevated to 56 per cent for the first time. Treatment with a low salt diet, digitalis, bed rest, intermittent oxygen, penicillin and gantrisin resulted in immediate improvement, but the ankle edema persisted. On October 24th a pneumoperitoneum was started with no improvement in symptoms. Maximum improvement had occurred by November 27th, and he was discharged on a low salt diet, digitalis, pneumoperitoneum and bronchodilator.

During the next year and a half he felt well on very limited activity at home. In April, 1952, ankle edema began to increase and mercupurine was given three times weekly. In May, 1952, the pneumoperitoneum was discontinued without noticeable change in the patient's condition.

The patient was kept comfortable at home, where he received excellent nursing care from his wife. He was completely bed-ridden for many months and finally expired in July, 1953. An autopsy was not performed.

Comment: On the first admission to the hospital the patient was believed to be in left ventricular failure and was treated initially with morphine and oxygen. Shortly after admission he became comatose; with caffeine and sodium benzoate, consciousness returned. On the second admission he was again given oxygen, and it was noted that the carbon dioxide combining power was rising. On the third admission right axis deviation was noted. It is probable that the coma on the first admission was a result of the suppression of ventilation secondary to morphine and oxygen. Over the next two years unmistakable signs of cor pulmonale developed.

The use of pneumoperitoneum in this patient had no apparent effect on lowering the arterial blood carbon dioxide or in improving the arterial blood oxyhemoglobin saturation. (Fig. 9.)

SUMMARY

After a brief discussion of the altered physiology and biochemical changes occurring in respiratory acidosis, the acid-base patterns in five patients with acute and three with chronic respiratory acidosis are reported. These patients all suffered from generalized obstructive emphysema. In the acute cases pulmonary infection and acute heart failure were superimposed, and in the chronic cases cor pulmonale was present. Vigorous treatment using simple and well recognized measures was uniformly successful in the patients with acute respiratory acidosis but was not adequate to reverse the acid-base abnormalities in the patients with chronic carbon dioxide retention. Various forms of treatment are discussed in relation to their effectiveness in increasing alveolar ventilation.

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Respiratory Acidosis*

I. Effects of Decreasing Respiratory Minute Volume in Patients with Severe Chronic Pulmonary Emphysema, with Specific Reference to Oxygen, Morphine and Barbiturates

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MANY physicians are familiar with the clinical disease states associated with metabolic acidosis. These are usually readily recognized and properly treated. On the other hand, acidotic states associated with abnormal respiration are frequently not suspected and may be confused with cardiac disease in the presence of dyspnea, orthopnea and edema.[1] Oxygen and morphine are frequently of therapeutic value in cardiac disease but may cause severe respiratory acidosis with coma and death in the presence of pulmonary emphysema. Uncompensated respiratory acidosis occurs because of reduced alveolar ventilation, resulting in an increase in the alveolar and arterial carbon dioxide tension.[2,3] An elevation of carbon dioxide tension with a lowering of the pH of arterial blood may occur with (1) a sudden diminution of the respiratory minute volume; or (2) a normal minute volume in the presence of insufficient alveolar ventilation.[4] In the latter instance the pulmonary physiologic dead space is well ventilated but not the alveoli.[5,6] In either case the ultimate disturbed physiologic state is ineffective alveolar ventilation.

The resting minute volume in patients with chronic diffuse pulmonary emphysema may be within or above the normal range, as a result of an increased respiratory rate; however, because of concomitant impaired alveolar ventilation, hypercapnia eventually appears with progression of the disease. In the presence of a high arterial carbon dioxide tension over a long period of time, the respiratory center becomes less sensitive to the gas.[7] With the partial loss of sensitivity to high tensions of carbon dioxide, hypoxia becomes a dominating factor in maintaining the respiratory minute volume.

Although hypoxia does not play a dominant role in the cause of dyspnea in these patients,[7,10] its presence serves as a stimulus to respiration in the severe disease state and may mean the difference between compensated and uncompensated respiratory acidosis.

This study was made to observe the effects of removal of the hypoxic stimulus to respiration in severe pulmonary emphysema and to demonstrate the untoward effects of morphine and barbiturates when used in patients with pulmonary emphysema.

METHOD

Twenty-six patients (Group A) with severe pulmonary emphysema were studied while breathing room air and subsequently while breathing 99.6 per cent oxygen for twenty minutes. The respiratory minute volumes were measured with the Tissot spirometer. The respiratory quotient was measured by the method of Haldane.[9] Femoral or brachial arterial blood samples were collected anaerobically for measurement of pH, per cent oxygen saturation and carbon dioxide content.[1] The pH was measured at 37.5°c. with the glass electrode.[15] Blood gas analyses were carried out by the method of Van Slyke and Neill.[11] The P_aCO_2 was calculated with the nomogram of Singer and Hastings.[12] Right heart catheterization was performed by the method of Cournand.[13] Effective alveolar ventilation was calculated by the standard formula[14] as follows:

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$$V_A = (Qb)(Rs)(P_B - P_AH_2O)\frac{(Ca_{O_2} - Cv_{O_2})}{P_{A_{CO_2}}}$$

V_A = alveolar gas volume per unit time
Qb = volume flow of blood or cardiac output 1/min.
Rs = respiratory quotient
P_B = barometric pressure
P_AH_2O = vapor pressure in the alveolar gas
Ca_{O_2} = concentration of oxygen in arterial blood
Cv_{O_2} = concentration of oxygen in venous blood
$P_{A_{CO_2}}$ = tension of carbon dioxide in alveoli

The statistical formulas used were the following:[16] To test the significance of differences from zero

$$t = \frac{\bar{x}}{\frac{\sigma}{\sqrt{n}}}$$

$$\sigma = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}{n-1}}$$

$$\gamma = \frac{\Sigma xy - \frac{(\Sigma x)(\Sigma y)}{n}}{\sqrt{\left(\Sigma x^2 - \frac{(\Sigma x)^2}{n}\right)\left(\Sigma y^2 - \frac{(\Sigma y)^2}{n}\right)}}$$

t = test of significance of difference from zero
$\bar{x}$ = mean values
σ = standard deviation
Σx^2 = sum of the square of the samples
$(\Sigma x)^2$ = square of the sum of the samples
n = the number of samples
x = a sample from the universe
y = a sample from the universe
γ = correlation coefficient

Two groups of patients who received morphine and barbiturates were studied with the same procedures as Group A (v.s.). With the thought that they had primary cardiac disease, five patients with pulmonary emphysema, dyspnea and dependent edema (Group B) were given morphine because of restlessness. Following sedation respiratory failure with an increase in cyanosis ensued and they were admitted to the hospital. Five other patients with severe pulmonary emphysema but without heart disease (Group C) were given barbiturates by resident physicians because of insomnia. Studies were done on these two groups during the period of respiratory depression and following clinical recovery from sedation.

RESULTS

In the twenty-six patients in Group A the mean value for nitrogen retention in the pulmonary alveoli was 4.0 per cent after a seven-minute period of breathing 99.6 per cent oxygen. The mean value for the oxygen saturation of the arterial blood was 83.5 per cent breathing room air. It was increased to 98.8 per cent during the twenty-minute period of breathing oxygen; $p < 0.01$. All patients physiologically saturated the arterial hemoglobin during the period of breathing oxygen, as shown in Table 1 and Figure 1.

TABLE 1
EFFECTS OF BREATHING 99.6 PER CENT OXYGEN IN PATIENTS WITH EMPHYSEMA
(*Group A*)

Patients	Minute Volume (L./min.)		Carbon Dioxide Tension (mm. Hg)		pH of Arterial Blood		Oxygen Saturation of Hemoglobin (%)	
	Before	During	Before	During	Before	During	Before	During
1	10.9	6.3	60.5	68.5	7.39	7.32	83.2	98.2
2	18.7	9.3	66.0	87.0	7.38	7.28	64.6	99.5
3	8.1	7.3	61.0	72.0	7.38	7.31	76.8	99.6
4	15.6	11.1	62.0	77.0	7.38	7.30	86.3	98.0
5	8.4	6.7	44.0	60.0	7.40	7.30	86.9	99.1
6	10.7	8.4	45.0	61.0	7.39	7.31	81.2	98.5
7	9.5	6.9	55.0	76.0	7.44	7.31	87.0	97.8
8	12.1	6.0	39.0	46.0	7.38	7.31	91.6	98.0
9	11.4	7.4	40.0	46.0	7.40	7.34	89.9	98.1
10	15.1	7.0	36.0	46.0	7.41	7.35	86.9	99.0
11	8.1	5.1	45.0	55.0	7.39	7.30	74.5	99.3
12	7.4	4.5	52.0	66.0	7.30	7.22	56.0	98.1
13	6.1	4.0	71.0	92.0	7.33	7.20	40.0	99.(
14	7.2	5.0	43.0	76.0	7.40	7.33	90.8	99.6
15	4.8	4.0	45.0	56.0	7.38	7.32	94.1	99.4
16	7.4	5.0	45.0	59.0	7.37	7.30	91.1	98.0
17	7.2	6.0	49.0	70.0	7.35	7.20	83.2	99.1
18	8.4	6.0	46.0	55.0	7.30	7.22	90.7	99.9
19	10.4	5.0	56.0	65.0	7.35	7.30	76.3	97.9
20	9.2	5.4	44.0	49.0	7.37	7.32	91.6	98.0
21	10.1	6.0	40.0	49.5	7.40	7.34	94.0	99.1
22	5.2	4.7	34.0	49.5	7.42	7.36	90.2	99.4
23	6.3	4.9	52.5	57.0	7.39	7.31	75.9	99.6
24	8.5	6.2	44.5	58.0	7.39	7.30	97.4	99.6
25	6.8	3.8	53.0	65.0	7.38	7.30	85.9	99.1
26	12.2	4.3	38.0	51.0	7.42	7.28	91.4	98.9

The mean respiratory minute volume was 9.4 L. per minute at rest. This was reduced to 6 L. per minute after breathing oxygen for a period of twenty minutes; $p < 0.01$. (Fig. 1.) After the hypoxic stimulus to respiration was eliminated, the tension of carbon dioxide rose from a mean level of 48.7 to 62.0 mm. Hg;

$p < 0.01$. (Fig. 2.) The pH of the arterial blood decreased from 7.38 to 7.29; $p < 0.01$. (Fig. 2.) Effective alveolar ventilation was decreased from 3.1 to 2.1 L. per minute; $p < 0.01$. (Fig. 3.)

carbon dioxide tension. There was a close correlation between the tension of carbon dioxide and the pH of the arterial blood; $r = 0.6060$, $p < 0.01$.

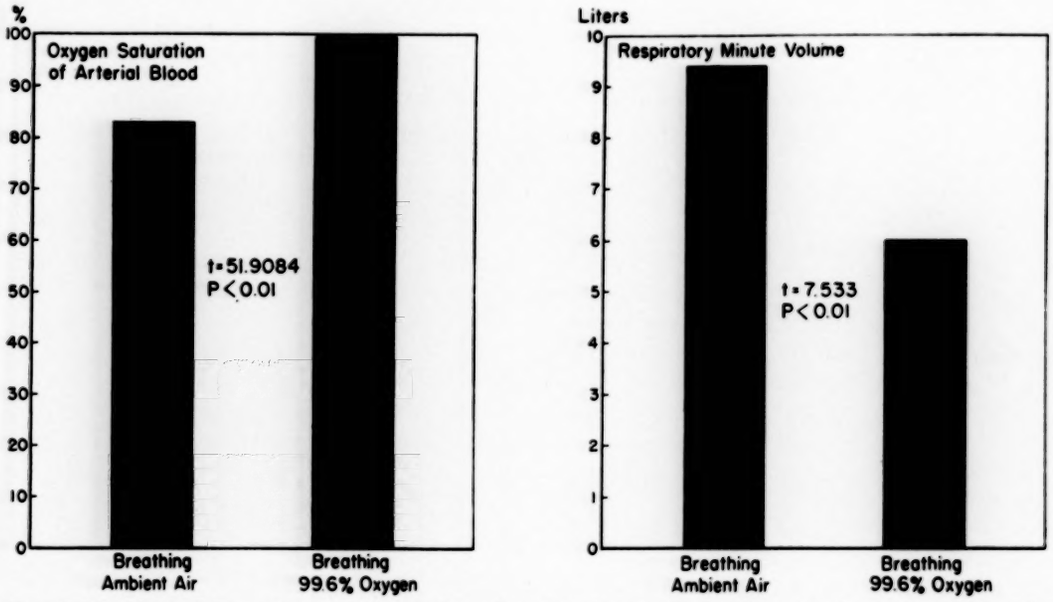

FIG. 1. Mean arterial oxygen saturation and respiratory minute volume of twenty-six patients with pulmonary emphysema while breathing ambient air and 99.6 per cent oxygen.

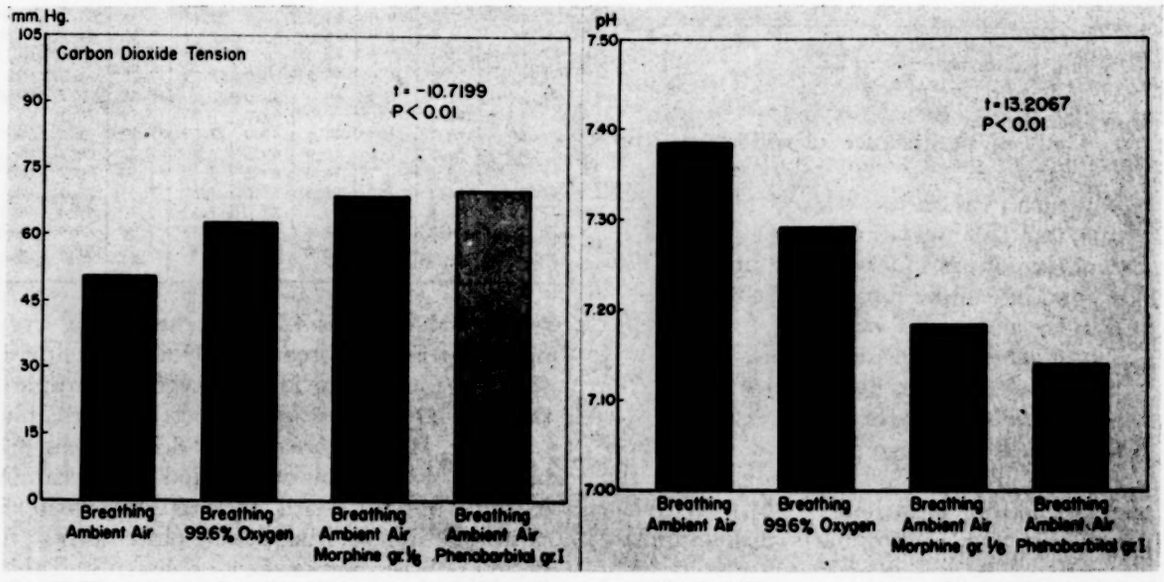

FIG. 2. The mean carbon dioxide tension and pH of the arterial blood of Group A while breathing ambient air and 99.6 per cent oxygen. The $PaCO_2$ and pH while breathing ambient air for Group B and Group C are included in columns 3, 4, 7 and 8.

There was a close correlation between the effective alveolar ventilation and tension of carbon dioxide in the arterial blood; $r = 0.7161$, $p < 0.01$. (Fig. 4.) There was no correlation between the respiratory minute volume and

The group of patients (Group B) with severe pulmonary emphysema who had been given morphine (gr. 1/6) had a mean minute volume of 3.9 L., which is well below the mean minute volume for patients with pulmonary emphysema

without sedation. (Fig. 5.) Upon recovery from sedation the mean respiratory minute volume was 7.5 L. per minute; $p < 0.01$.

The carbon dioxide tension decreased from 74.0 mm. Hg to a level of 59.5 mm. Hg after recovery from respiratory center depression.

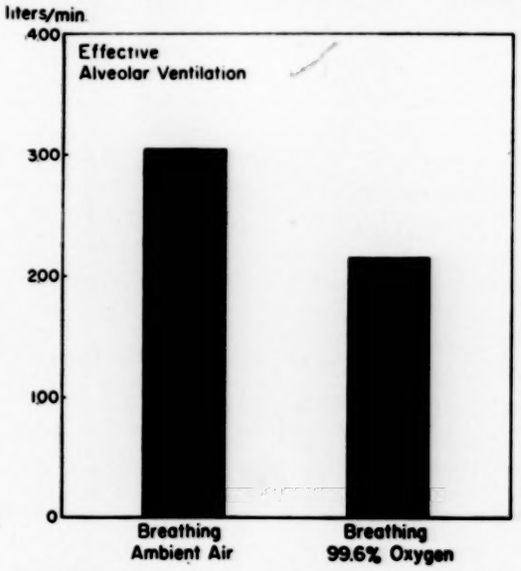

FIG. 3. The mean effective alveolar ventilation for Group A while breathing ambient air and while breathing 99.6 per cent oxygen.

TABLE II

RESPIRATORY MINUTE VOLUME, pH, P_aCO_2 AND PER CENT OXYGEN SATURATION OF ARTERIAL BLOOD FOLLOWING MORPHINE GR. 1/6 OR PHENOBARBITAL GR. 1 AND FOLLOWING RECOVERY WHILE BREATHING AMBIENT AIR

Patient No.	Minute Volume (L./min.)		Carbon Dioxide Tension (mm. Hg)		pH of Arterial Blood		Oxygen Saturation of Hemoglobin (%)	
	Narcosis	Recovery	Narcosis	Recovery	Narcosis	Recovery	Narcosis	Recovery
(Group B)								
1.	3.1	7.0	92.0	71.0	7.10	7.33	35.0	50.0
2.	5.0	9.3	77.2	62.1	7.25	7.38	75.0	87.1
3.	4.5	7.0	67.4	51.9	7.29	7.40	56.0	85.0
4.	2.8	5.8	65.4	53.4	7.23	7.38	78.9	86.0
5.	4.3	8.3	68.0	59.0	7.28	7.39	58.0	83.2
Mean	3.9	7.5	74.0	59.5	7.23	7.38	60.6	78.7
(Group C)								
1.	2.0	8.0	100.0	75.0	7.00	7.20	40.0	65.0
2.	3.5	6.0	64.0	56.0	7.20	7.38	50.0	76.1
3.	2.3	7.1	80.1	50.0	7.10	7.33	60.1	80.0
4.	4.0	8.0	75.2	45.0	7.25	7.39	75.0	85.0
5.	3.1	7.1	89.0	68.0	7.10	7.30	75.0	81.2
Mean	2.98	7.2	81.7	58.8	7.13	7.32	60.0	77.4

(Fig. 2.) The pH initially was 7.23, whereas during the more normal period of respiration it rose to 7.38 (Table I, Fig. 2), which is within the normal range of 7.40 ± 0.02.[15]

Oxygen saturation of the hemoglobin was 60.6 per cent during morphine narcosis; it rose

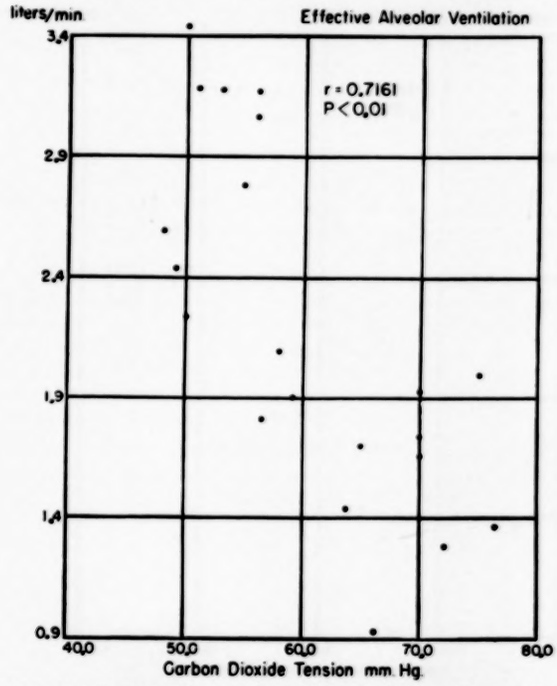

FIG. 4. The correlation of carbon dioxide tension with effective alveolar ventilation in twenty-one of the patients with pulmonary emphysema included in Group A.

to a mean level of 78.7 per cent with an increased minute volume and more efficient alveolar ventilation. (Fig. 5.)

A third group of patients (Group C) (Table II) received phenobarbital (gr. 1) because of insomnia. In a manner similar to the effect of morphine, the respiratory center was depressed with a further increase in uncompensated respiratory acidosis. The respiratory minute volume during sedation was diminished 4.22 L.; $p < 0.01$. (Fig. 6.) The carbon dioxide tension of arterial blood rose 22.9 mm. Hg; $t = 7.29$, $p < 0.01$ (Fig. 2); with a concurrent decrease of the pH from 7.38 to 7.13. (Fig. 2.) Following recovery from sedation with an increase in the minute volume and more efficient alveolar ventilation, the oxygen saturation of the hemoglobin in the arterial blood rose 17.4 per cent; $p < 0.02$. (Fig. 6.) During the period of recovery from sedation, respiratory stimulants were used but oxygen was withheld as it would have added to the severity of respiratory depression.

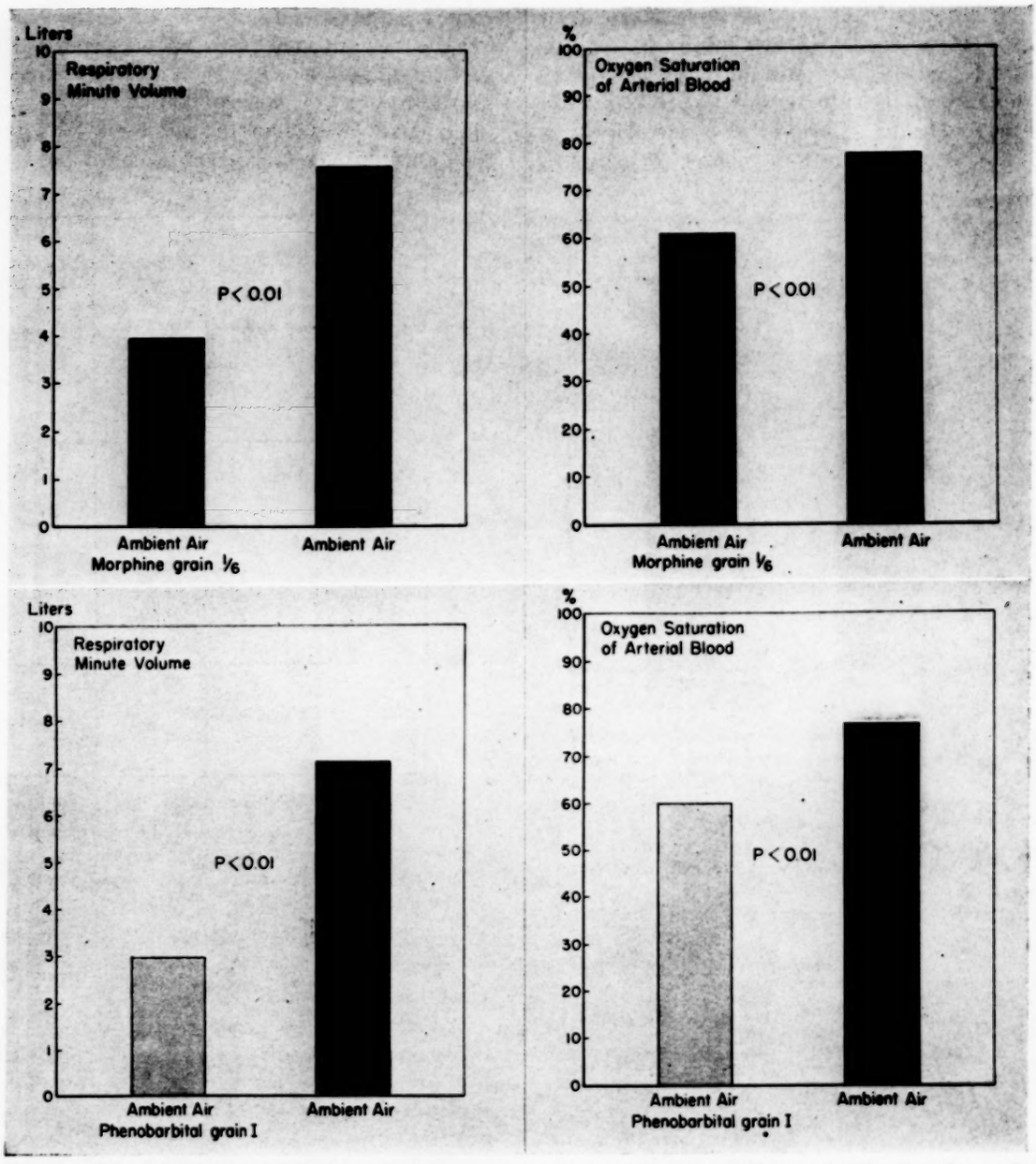

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FIG. 5. The respiratory minute volume and percentage oxygen saturation of the arterial blood in Group B breathing room air during and following recovery from sedation with morphine, gr. 1/6.

FIG. 6. The respiratory minute volume and percentage oxygen saturation of the arterial blood in Group C breathing ambient air during and following recovery from phenobarbital, gr. 1.

COMMENTS

A group of patients with severe pulmonary emphysema with hypoxemia at rest was selected for study because it has been noted that their respiratory centers are less sensitive to increased carbon dioxide tension than those of normal persons.[2,7]

When an emphysematous patient has decreased responsiveness to increased carbon dioxide tension and hypoxia has developed, the latter becomes a strong respiratory stimulus. As the pulmonary parenchyma is destroyed, ventilatory and diffusional defects in the alveolar gas phase increase in severity. Inefficient ventilation is attributed to increased physiologic dead space and unequal ventilation of the pulmonary alveoli. Diffusion of oxygen through the venti-

lated alveolar walls is not impaired to any great extent because practically 100 per cent oxygen saturation of the arterial blood is attained when these patients breathe 99.6 per cent oxygen for twenty minutes.

Carbon dioxide diffuses through the alveolar walls approximately thirty times as readily as oxygen; however, its rate of diffusion through the gaseous phase in the alveoli is slower. With an increase in physiologic dead space and in the presence of uneven alveolar ventilation, the tension of carbon dioxide rises not only in the alveoli but in the blood.

In normal lungs where most of the alveoli are well ventilated in the presence of normal physiologic dead space, the carbon dioxide tension changes in alveoli, as well as in blood, are closely correlated with the minute volume. In patients with pulmonary emphysema with uneven alveolar ventilation and an increased physiologic dead space, the respiratory minute volume may be within normal or above normal limits with an increased respiratory rate but ventilation of the alveoli is inadequate. If for some reason the minute volume is decreased, either by a decrease in respiratory rate or in tidal volume, in the presence of an existing increased physiologic dead space and unevenness of alveolar ventilation, uncompensated respiratory acidosis will develop.

In normal persons, breathing 99.6 per cent oxygen does not significantly decrease the respiratory minute volume. However, in patients having severe pulmonary emphysema with hypoxemia, with a chronic increase of the tension of carbon dioxide in the arterial blood, sudden removal of the hypoxic stimulus causes a marked decrease in the respiratory minute volume. Inadequate alveolar ventilation is more severe and uncompensated respiratory acidosis is the immediate result. If the patient respires 99.6 per cent oxygen for several hours, the rise in P_aCO_2 and decrease in pH of the arterial blood leads to the development of severe respiratory acidosis and coma which may lead to death. It should be emphasized at this point that a patient with pulmonary emphysema may become adapted to breathing oxygen at a high tension if the gas is administered to him in a stepwise fashion. Sudden changes of the oxygen tension in the respired air are to be avoided in patients whose primary stimulus to respiration is hypoxia.

In patients with severe chronic pulmonary emphysema, the minute volume and more effective alveolar ventilation is maintained by an increase in the respiratory rate. Morphine decreases the respiratory rate progressively in man. This effect of the drug eliminates the only remaining compensatory respiratory mechanism by which the patient prevents uncompensated respiratory acidosis. Morphine also depresses the response of the carotid body to hypoxia, pH and P_aCO_2.[18] There are three reasons why morphine adversely affects patients with emphysema: (1) The respiratory center in the presence of morphine responds less rapidly to higher levels of P_aCO_2 and a lower pH. (2) The carotid body fails to stimulate respiration normally in the presence of further hypoxemia. (3) The central nervous system is depressed to the extent that the Hering-Breuer reflex fails adequately to assist respiration in the normal way.

Barbiturates are frequently used to induce sleep in the patient with insomnia. In the patient with severe chronic pulmonary emphysema, these drugs are dangerous even in small doses because they depress the respiratory rate and lead to uncompensated respiratory acidosis, as shown in Table II.

SUMMARY

In patients with prolonged elevation of P_aCO_2 the respiratory center loses its normal degree of sensitivity to carbon dioxide. Hypoxia then becomes the dominant stimulus to respiration.

This stimulus to respiration is removed by breathing 99.6 per cent oxygen. The respiratory minute volume and effective alveolar ventilation are then decreased significantly. Subsequently the P_aCO_2 becomes elevated and the pH of the blood is depressed to a lower level. Uncompensated respiratory acidosis supervenes. In the more diseased states coma ensues.

Morphine and barbiturates in small doses may depress the minute volume and effective alveolar ventilation in patients with pulmonary emphysema. Respiratory acidosis with coma readily develops in these patients because they retain large quantities of carbon dioxide in the pulmonary alveoli and arterial blood.

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A Physiologic Evaluation of the Effects of Diaphragmatic Breathing Training in Patients with Chronic Pulmonary Emphysema*

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NUMEROUS clinical reports have appeared presenting diaphragmatic breathing training, or abdominal breathing exercises, as effective adjuncts in the treatment of patients with asthma and emphysema.[1-10] However, there has been no systematic evaluation of this therapy by physiologic methods.

The principal objective of this investigation was to determine the specific benefits of this therapeutic procedure, quite apart from the known benefits of other more widely used therapeutic methods. The objective approach became necessary because of the difficulty in evaluation of subjective responses which are a natural consequence of an improved patient-doctor relationship, itself a direct result of an aggressive therapeutic approach to chronic pulmonary disease.

This report deals with the results of such a study in patients with severe chronic pulmonary emphysema.

CLINICAL MATERIAL

Patients were selected for training in diaphragmatic breathing after they had achieved maximal benefit from other commonly accepted methods of treatment recommended as optimal by Barach[18] and Segal.[19] Such optimal therapy included: (1) effective treatment of infection and bronchial obstruction by appropriate oral or parenteral antibiotics with bronchodilator and wetting agent nebulizations; (2) instruction in the proper use of the nebulizer; (3) training in the proper technic for more effective cough and postural drainage; (4) abstinence from smoking whenever possible. In some instances it was necessary to continue such treatment for as long as two to three months until a state of maximal improvement was attained. The data presented were obtained from twenty-four patients who were studied prior to, and again six weeks to two months after, a period of training in diaphragmatic breathing.

Certain clinical information about the patients in this series is listed in Table I. The most frequent underlying disease was chronic generalized obstructive bronchitis. The designation asthmatic bronchitis is used to indicate those patients with obstructive bronchitis who presented a clinical picture of paroxysmal wheezing dyspnea but in whom definite evidence of specific extrinsic allergic asthma could not be established. The diagnosis pulmonary fibrosis is based principally on roentgenographic evidence. Unless otherwise indicated, the fibrosis was considered moderate. In some instances in which only slight fibrosis was roentgenographically apparent respirographic evidence of a restrictive type of ventilatory pattern was used as additional support for the designation of fibrosis.

Five patients (W. B., T. G., C. W., G. C. and F. B.) had definite right heart failure one or more times while under observation. Compensation had been restored prior to the study periods. W. B., T. G., C. W. and F. B. at some time also had left heart failure.

METHODS

Maximum diaphragmatic excursion was measured fluoroscopically from maximum expiration to maximum inspiration, particular care being taken to avoid distortion. Measurements had to

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TABLE 1

Case	Age (yr.)	Ht. (in.)	Body Surface Area (M^2)	Clinical Information	Duration (yr.)	Maximum Diaphragm Excursion (cm.)		Respiratory Rate/Min.		Tidal Volume (cc.)		Resting				Exercise					
												Liters Ventilation (M^2)		O_2 Removal Rate (cc.)		Liters Ventilation (M^2)		O_2 Removal Rate (cc.)		Duration Postexercise Dyspnea (sec.)	
						Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.
W. B.	44	75	1.8	Bronchiectasis; fibrosis; cor pulmonale; hemoptysis	20	0	5	16	10	650	1200	5.8	8.4	34.6	28	....	....	....	....	...	...
T. G.	61	68	1.8	Asthmatic bronchitis; fibrosis; cor pulmonale; hemoptysis	19	2	4	16	11	365	560	3.3	3.4	42	41	7.7	10	60	62	120	90
E. S.	35	64	1.5	Bronchiectasis; fibrosis	7	2	3	18	12	440	692	5.3	5.6	29	28	13.2	13.4	46	47	65	65
E. H.	66	69	1.8	Asthmatic bronchitis; fibrosis, marked	25	1	3.5	16	10	594	960	5.3	5.5	24	25	....	....	....	....	...	...
C. L.	60	68	1.7	Asthmatic bronchitis; fibrosis, slight	10	1	4	18	14	445	522	4.7	4.3	36.2	44.4	11	13.5	34	50	110	90
T. A.	48	71	1.9	Bronchitis; fibrosis	7	1.5	4	20	16	305	338	3.1	2.9	33	38	8.4	9.6	60	63	110	65
C. W.	61	70	1.6	Bronchitis; cor pulmonale; fibrosis, marked	22	0	4.5	26	15	370	415	6.0	3.8	19	32	7.9	9.7	44	46	120	100
J. A.	60	71	1.7	Asthma; bronchitis	33	3	5	11	8	525	612	3.5	3.0	42.6	54.4	6.9	8.1	70	78	85	65
J. P.	43	69	1.9	Asthmatic bronchitis	5	1	4	12	12	492	520	3.1	3.3	45	41	9.5	11	65	68	70	65
O. H.	57	66	1.7	Asthmatic bronchitis	35	3	5	15	14	510	715	4.6	6.1	35.2	30.2	12.7	12.2	57	63	75	60
J. R.	60	69	1.7	Asthmatic bronchitis; fibrosis	24	1	4	15	15	420	618	3.9	5.2	35.7	34.7	9.5	10.1	60	64	100	70
M. W.	60	69	1.5	Asthmatic bronchitis	10	2	4	11	11	443	807	3.3	5.6	36.5	32	10	12.9	40	51	85	70
W. J.	58	70	1.9	Asthmatic bronchitis	4	3	4.5	15	14	550	714	4.3	5.9	32.7	30.5	15.8	16	44	45	55	50
G. C.	34	70	1.6	Bronchiectasis; fibrosis; cor pulmonale; hemoptysis	15	1	4.5	16	13	434	560	4.3	4.5	34	35	9.7	9.9	36	61	85	50
W. L.	53	68	1.6	Bronchitis; fibrosis, marked	10	3.5	5.5	20	10	432	720	5.1	4.4	27	32	16.6	17.4	40	42	100	75
F. B.	30	67	1.6	Asthma; fibrosis; cor pulmonale; hemoptysis; bronchiectasis	25	2	4.5	15	7	395	715	3.7	3.1	36	51	12.7	8.0	40	63	90	75
B. R.	54	71	1.8	Bronchitis; fibrosis, slight	11	3	5	16	16	735	740	6.7	5.9	25.4	29.3	15	15	33	45	105	85
M. M.	59	63	1.6	Bronchitis; fibrosis, slight pleuritis	6	2.5	6	15	13	500	538	4.7	4.4	29	34.3	11.3	12.5	50	55	85	65
F. C.	28	70	1.7	Asthma; bronchitis	10	2	6	18	13	567	615	6.0	4.7	27.2	33.3	16.5	14.5	31	44	75	50
E. D.	29	68	1.6	Asthma; bronchitis	25	1	6	36	16	314	522	6.9	4.7	25.5	32	17.5	13.7	33	44	120	75
J. G.	61	68	1.7	Bronchitis	13	2	6	15	10	635	639	5.7	3.8	28	38.2	13.6	11.3	34	65	80	65
W. P.	64	71	1.9	Bronchitis	32	3	4.5	20	17	495	556	5.4	5.1	27	29	16.7	16	32	34	105	65
J. W.	57	71	1.9	Asthma; bronchitis; arthritis	25	3	6	16	16	615	594	5.0	4.9	29	28	9.2	8.5	62	68	75	70
L. H.	55	72	1.7	Bronchitis	2	2	5.5	19	7	368	600	4.2	2.5	35	54	15.9	10	47	61	105	75
Mean	51 5	69.1	1.7		16.5	1.8	4.8	17.3	12.2	483	645	4.8	4.6	32	36	12	11.9	46.3	55.4	92	70
SDmd						1.1		4.79		143.0				6.63				8.65		12.99	
SEmd						0.23		0.98		29				1.35				1.84		2.77	
p						0.01		0.01		0.01				0.02				0.01		0.01	
Normal value						5 to 8 cm.		12 to 16 per min.		400–500 cc.		3.2–4.5 L./M^2		30–40 cc. per L. Vent.		10–16 L./M^2		40–50 cc. per L. Vent.		* 60 sec.	

be duplicated repeatedly and in most instances to the satisfaction of at least two observers.

Pulmonary function studies were all performed early in the morning. In order to avoid the distress of coughing and expectoration the patients were always given their usual morning medications, consisting of a nebulized inhalation of 0.3 to 0.8 cc. aeralone compound or isuprel® with 2 to 6 cc. of 0.01 per cent or 0.001 per cent aqueous zepherin chloride® in 10 per cent propylene glycol at 6 A.M. This was followed by the ingestion of 0.2 gm. non-enteric coated aminophylline at 7 A.M. The patients were brought to the laboratory by 7:30 A.M. and permitted to rest in a semi-supine position for at least one-half hour, during which time the patient was acquainted with the apparatus and procedure.

In order to eliminate the element of bronchospasm and retained secretions as much as possible, ventilation studies were performed before and after the administration of eight to twelve inhalations of nebulized aeralone compound using a technic described elsewhere.[11] In every case the data reported are those obtained after such bronchodilator therapy.

Ventilation studies were made using a Collins' nine-liter respirometer with ventilographic attachment. A resting ventilation tracing was made from which oxygen consumption, oxygen removal rate, respiratory rate and tidal volume could be calculated. The one-minute Standard Exercise Test of Baldwin and associates[12] was then performed, and from the tracing obtained the exercise ventilation response as well as the oxygen consumption and oxygen removal rate was determined. The duration of postexercise dyspnea was timed while the patient was still breathing from the spirometer and recorded to the nearest five-second interval. The soda lime absorber and valves were then removed and the dynamic lung volumes and maximum breathing capacity (MBC) were measured. All values were appropriately corrected to BTPS or STPD.[13] The vital capacity (VC) was repeated as often as necessary to obtain checks of maximal values within 200 cc. The MBC determinations were also repeated as indicated to obtain checks of maximal values within 5 L. The VC prediction formula of Baldwin et al. was used except for the three-second vital capacity (3VC) which was found by us to be normally >95 per cent of the VC with this apparatus. Predicted MBC's were determined from the formula of Motley.[14] These predicted values best correlate with normal values obtained in this laboratory.

Arterial blood studies were made either at the same time or on the following day. Arterial blood samples were obtained with the patient at rest and immediately after one minute of one-step exercise[12] with an indwelling Cournand needle in one of the brachial arteries.

Blood gas analyses for oxygen and carbon dioxide content were performed by the manometric method of Van Slyke and Neill. Arterial oxygen per cent saturation was calculated by the method described by Comroe.[13] Blood pH values were determined in a constant temperature system at 37.5°C. using the closed glass electrode system and the Cambridge electron-ray pH meter. Arterial pCO_2 values were read from the nomogram of Singer and Hastings[15] using the determined CO_2 content, hematocrit and pH.

Following preliminary studies diaphragmatic breathing training was instituted according to the general technic described by the Asthma Research Council of England.[3] Certain important modifications which will be presented elsewhere[16] were introduced. Six weeks to two months later the patients were restudied.

RESULTS

The data on diaphragmatic excursion, resting and exercise ventilation are listed in Table I. Several very significant improvements are noted. There was an increase in maximum diaphragmatic excursion of 3.0 cm. ($p < 0.01$). This was accompanied by a striking combination of findings. Although the total resting ventilation was not significantly changed, the respiratory rate showed a decrease (5.1/min., $p < 0.01$), the tidal volume was increased (162 cc., $p < 0.01$) and the resting oxygen removal rate was also increased (4 cc./L. of ventilation, $p < 0.01$). After diaphragmatic training there was a definite increase in O_2 removal rate during exercise (9.1 cc./L. ventilation, $p < 0.01$). When all twenty-four patients are considered in one group the exercise ventilation response was not significantly changed. If on the other hand (Table III) those patients whose MBC was at all times less than 40 per cent of the predicted value (an MBC of less than 40 per cent in these patients indicates a severe degree of emphysema)[17] are considered separately, it will be noted that the ventilatory response to exercise showed significant improvement following dia-

phragmatic breathing training. Two other patients (W. B. and E. H.) whose MBC's were less than 40 per cent were unable to perform the exercise prior to the training period.

Table II is arranged to show the changes in dynamic lung volumes that occurred with diaphragmatic training. With regard to the maximum expiratory pressure (MEP),[17] the patients in this series showed low values, as might be expected. A very small but significant increase was observed in the follow-up studies (16 mm. Hg, $p < 0.01$).

In patients with asthma or pulmonary emphysema the expiratory reserve volume (ERV) after a deep inspiration is known to be decreased as compared to this volume when measured after a tidal inspiration. For this reason the ERV was measured from the respiratory mid-position after a tidal breath, as shown in Figure 1. This figure further illustrates how the inspiratory capacity (IC) and expiratory vital capacity (VC) were measured.

In this series there was an average increase of 600 cc. (23 per cent) in the vital capacity ($p > 0.01$). This was found to be due principally to an increased inspiratory capacity (450 cc., $p < 0.01$). There was a small increase (116 cc.) in the ERV which was not significant because of

TABLE II

Case	Maximum Expiratory Pressure mm. Hg		Inspiratory Capacity Liters		Expiratory Reserve Volume cc.		Expiratory Vital Capacity				Three-second Vital Capacity				Maximum Breathing Capacity			
							Liters (%) Pre.		Liters (%) Post.		Liters (%) Pre.		Liters (%) Post.		Liters (%) Pre.		Liters (%) Post.	
	Pre.	Post.	Pre.	Post.	Pre.	Post.												
W. B.	...	...	1.1	2.9	800	2,100	1.6	37	4.5	107	0.6	14	1.2	26	19	14	35	26
T. G.	95	90	1.86	1.96	1,008	750	2.6	70	2.6	70	1.2	35	1.5	44	29	30	33	34
E. S.	100	115	2.0	2.0	580	620	2.5	63	2.6	66	1.4	37	1.6	38	38	32	39	33
E. H.	...	...	1.1	1.6	800	600	1.6	45	2.0	57	0.8	24	1.5	46	21	22	25	26
C. L.	...	...	1.3	1.85	1,000	1,600	2.4	66	3.1	85	1.1	32	1.8	52	21	19	30	26
T. A.	130	150	2.3	2.7	810	726	2.7	67	2.9	73	1.5	38	1.6	42	38	27	43	31
C. W.	...	...	0.9	1.5	820	1,170	1.5	40	2.1	57	0.9	26	1.1	32	15	17	26	29
J. A.	115	115	2.35	2.61	1,300	1,380	3.3	87	3.4	89	1.5	41	1.5	41	29	26	39	35
J. P.	120	120	2.25	2.74	560	376	3.0	74	3.1	75	1.5	40	1.9	50	42	30	58	41
O. H.	75	100	2.8	3.0	825	830	3.5	95	3.6	98	2.1	58	2.3	61	65	56	84	72
J. R.	120	120	1.6	1.8	538	560	2.1	60	2.3	63	1.3	39	1.4	43	42	37	51	45
M. W.	80	85	1.86	2.31	918	829	2.5	73	2.7	78	1.5	45	1.6	49	48	48	53	53
W. J.	20	140	3.38	3.70	1,420	1,010	4.6	122	4.7	125	2.2	61	2.2	61	79	61	82	63
G. C.	140	160	1.76	2.48	100	362	1.9	45	2.1	51	1.2	30	1.4	36	39	30	52	40
W. L.	100	90	1.41	1.48	715	910	1.8	46	2.0	51	1.5	41	1.6	44	34	30	42	38
F. B.	60	80	1.42	2.06	780	404	1.9	48	2.6	63	1.2	30	1.7	44	57	44	78	60
B. R.	80	90	2.1	2.24	770	814	2.7	70	2.9	75	1.8	50	2.2	59	52	41	74	59
M. M.	140	160	1.8	2.37	174	350	2.2	65	2.7	79	1.6	47	1.9	58	44	41	61	56
F. C.	140	150	2.45	2.68	1,100	1,380	3.2	72	4.1	92	1.7	41	3.7	88	54	38	123	87
E. D.	80	100	1.13	2.39	594	888	1.4	34	3.4	83	1.4	35	2.8	70	58	44	104	79
J. G.	100	110	2.2	2.55	1,500	1,610	3.2	90	4.1	100	1.6	46	2.0	61	32	34	51	54
W. P.	80	100	3.24	3.52	1,910	1,820	4.9	131	5.0	134	3.0	84	3.1	87	81	65	94	75
J. W.	110	140	3.0	3.54	570	1,430	3.1	80	5.0	130	2.1	58	3.1	84	56	43	86	66
L. H.	100	90	2.38	2.58	1,040	900	3.2	81	3.3	83	1.8	47	1.9	50	41	35	48	40
Mean	99	115	1.99	2.44	860	976	2.6	69	3.2	83	1.5	42	1.9	53	43	36	59	49
SDmd	27.18		0.114				0.730				0.432				15.08			
SEmd	6.08		0.023				0.149				0.088				3.08			
p	<0.01		<0.01				<0.01				<0.01				<0.01			
Normal	141 ± 32		75–80% V.C.		20–25% V.C.		100%				100%				100%			

the large standard deviation of the differences. Three-second vital capacity (3VC) increased 26.7 per cent ($p < 0.01$) and the maximum breathing capacity (MBC) increased 37.2 per cent ($p < 0.01$) after training in diaphragmatic breathing.

TABLE III
EXERCISE VENTILATION RESPONSE OF PATIENTS WITH MBC LESS THAN 40% OF PREDICTED

Case	MBC % of Predicted		Exercise Ventilation (L./min/M²)	
	Pre.	Post.	Pre.	Post.
T. G.	30	34	7.7	10.0
E. S.	32	33	13.2	13.4
C. L.	19	26	11.0	13.5
T. A.	27	31	8.4	9.6
C. W.	17	29	7.9	9.7
J. A.	26	35	6.9	8.1
W. L.	30	38	16.6	17.4
Md	6.4		1.43 L.	
p			<0.01	

The results of arterial blood studies are listed in Table IV. There was a small but significant ($p < 0.01$) increase in the arterial O_2 per cent saturation both at rest and immediately after exercise. Likewise, there were small but significant ($p < 0.01$) decreases in arterial pCO_2 both at rest and after exercise. Finally, the hematocrit declined significantly (−3 per cent, $p < 0.01$).

COMMENTS

These data emphasize that diaphragmatic breathing training results in increased diaphragmatic excursion which in turn provides a more effective tidal volume at a slower respiratory rate with no significant change in total ventilation. When total ventilation is diminished prior to treatment, an increase usually results after diaphragmatic training. The increased inspiratory capacity noted in this study suggests a lowering of the respiratory mid-position and decrease in functional residual capacity. The net result of these changes is more effective alveolar ventilation as indicated by increased arterial O_2 per cent saturation and decreased pCO_2. The increased 3VC and MBC indicate improved velocity air flow which plays an all-important role in the increased exercise tolerance. Objective evidence of increased exercise tolerance is indicated by decreased postexercise dyspnea time and increased postexercise O_2 per cent saturation.

There are certain important considerations that must be kept in mind in the evaluation of these data, since certain pretraining events tend to mask the beneficial effects that can be measured. Frequently it was difficult to keep treated patients from teaching untreated patients about diaphragmatic breathing, so that some of the patients had considerable orientation at the time of the pretreatment studies. In the process of conducting effective instruction in improved coughing, postural drainage technics and nebulization, physical skills which are critically concerned in diaphragmatic breathing training are unavoidably developed.

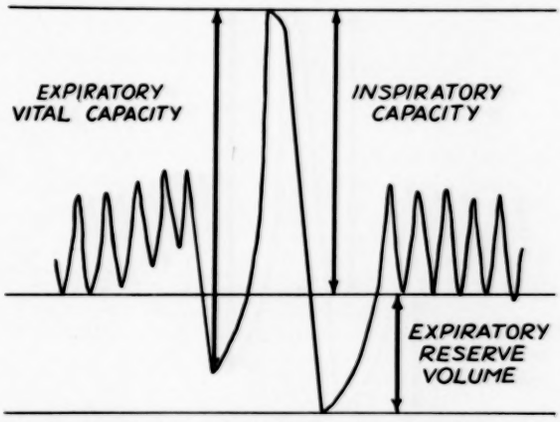

FIG. 1. Respiratory tracing indicating method used in recording and measuring dynamic lung volumes. This figure further illustrates the air trapping that follows a deep inspiration, which is so characteristic of tracings obtained from patients with emphysema who have an obstructive type ventilatory defect.

Clinically it is apparent that effective diaphragmatic training usually results not only in simple improvement of ventilation but also in in a more effective cough mechanism with improved evacuation of bronchial secretions. Better control of the almost inevitably recurrent bronchial infections is thereby achieved.

Experience with this method of treatment has indicated that in patients with less severe disease diligent continuation of this therapy will frequently produce striking recovery of function. Patients F. C. and E. D. are examples of this situation. Both of these young men were victims of severe asthma with bronchitis and emphysema. Both had been completely disabled and unable to work for several years. Both had been

treated with intensive drug therapy, including adrenal steroids, with improvement which was invariably evanescent. Diaphragmatic breathing training was started when they were in a state of optimal improvement, which in each case represented a state of well-being that was as good as or better than had been experienced in several years. Neither of these individuals was very enthusiastic about undertaking diaphragmatic breathing training because of their discouragement with repeated therapeutic failures. The studies reveal that whereas both had practically no effective diaphragm excursion before training, after training they each had 6 cm. excursion which was accompanied by remarkable improvement in all functions. More than a year after discharge both of these patients had maintained improvement in spite of occasional recurrent asthma and both were working. Neither had been hospitalized since discharge.

TABLE IV

Case	Arterial O_2 % Saturation				Arterial pCO_2 mm. Hg				Arterial pH				Hematocrit (%)	
	Resting		Exercise		Resting		Exercise		Resting		Exercise		Pre.	Post
	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.		
W. B.	60	71	..	..	69	59	..	..	7.38	7.42	....	....	58	50
T. G.	76	79	66	75	55	50	59	53	7.36	7.39	7.33	7.36	58	54
E. S.	..	..	..	..	..	..	..	..	....	....	....	....	49	47
E. H.	85	87	..	..	51	46	..	..	7.41	7.43	....	....	49	44
C. L.	84	86	78	87	70	60	73	53	7.36	7.37	7.35	7.41	51	48
T. A.	86	88	78	84	56	50	55	48	7.40	7.41	7.37	7.58	51	46
C. W.	89	90	85	86	49	40	53	43	7.42	7.45	7.40	7.43	49	46
J. A.	..	..	..	..	..	..	..	..	....	....	....	....	48	46
J. P.	..	..	..	..	..	..	..	..	....	....	....	....	43	43
O. H.	..	..	..	..	..	..	..	..	....	....	....	....	41	40
J. R.	..	..	..	..	..	..	..	..	....	....	....	....	39	39
M. W.	88	92	82	90	38	37	39	33	7.46	7.45	7.42	7.43	44	42
W. J.	93	94	93	93	39	38	37	37	7.44	7.43	7.43	7.42	42	40
G. C.	62	84	52	78	50	43	52	48	7.42	7.39	7.40	7.38	51	47
W. L.	86	91	82	88	46	39	45	37	7.41	7.42	7.39	7.40	49	46
F. B.	70	85	51	78	48	42	43	40	7.45	7.40	7.44	7.39	47	44
B. R.	..	..	..	..	..	..	..	..	....	....	....	....	40	38
M. M.	89	92	89	93	38	37	39	36	7.44	7.44	7.45	7.44	42	41
F. C.	87	95	86	96	46	37	48	36	7.40	7.42	7.39	7.43	46	44
E. D.	88	94	91	95	46	40	42	38	7.41	7.43	7.44	7.43	43	42
J. G.	..	..	..	..	..	..	..	..	....	....	....	....	45	43
W. P.	..	..	..	..	..	..	..	..	....	....	....	....	44	44
J. W.	..	..	..	..	..	..	..	..	....	....	....	....	46	44
L. H.	..	..	..	..	..	..	..	..	....	....	....	....	45	44
Mean	82	88	78	87	50	44	49	42	7.41	7.42	7.40	7.43	47	44
SDmd	6.12		7.99		3.50		5.26		.008		.066		1.93	
SEmd	1.64		2.31		0.94		1.51		.002		.019		0.395	
p	<0.01		<0.01		<0.01		<0.01		<0.01		<0.1		<0.01	
Normal	>96%				37–40 mm				7.36–7.45				42–45	

emphysema who were studied before and after a six- to eight-week period of diaphragmatic breathing training which was instituted only after a state of optimal improvement had been achieved with long-term, intensive treatment by conventional measures.

Increased diaphragmatic excursion, accomplished by this training, resulted in a striking increase in tidal volume at a lower respiratory rate and respiratory mid-position. As a result

SUMMARY AND CONCLUSIONS

Pulmonary function data are presented on twenty-four patients with chronic pulmonary

of these changes more effective alveolar ventilation was accomplished without significant increase in total ventilation except in those instances in which it was decreased prior to training.

Improved alveolar ventilation was indicated by increased O_2 removal rate, increased arterial oxygen saturation, decreased arterial pCO_2 and increased exercise tolerance with less dyspnea.

This study indicates that diaphragmatic breathing training is an effective adjunct in the treatment of pulmonary emphysema and that such training can be expected in most instances to produce objective improvement in pulmonary function.

Acknowledgments: The author is particularly grateful to Miss Maurine Giese and Mr. Russell Horn who gave valuable technical assistance. Miss Atha Lee Scott, physiotherapist, provided enthusiastic interest and aid in the supervision and instruction of the patients. The valuable assistance given by Dr. Nancy Wu, who performed a major portion of the statistical analyses, is sincerely appreciated and the helpful advice and criticisms provided by Dr. Carleton B. Chapman during the preparation of the manuscript is gratefully acknowledged.

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Chronic Bronchitis and Emphysema*

Significance of the Bacterial Flora in the Sputum

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SEVERAL authors have recently published data concerning the bacteria found in the sputum of patients with chronic bronchitis.[2,5,7] These authors have indicated the relative frequency in the sputum of several different bacterial species, notably Hemophilus influenzae, pneumococcus and Staphylococcus aureus which are regarded as being pathogenic or potentially so. May[4] has stressed the variable results obtained in sampling the sputum from patients with chronic bronchitis, and by using a multiple sampling technic for each specimen has correlated the presence of pneumococci and H. influenzae with the presence also of pus in the sputum. The present investigation was carried out in the hope of obtaining data concerning the source of pathogenic bacteria found in the sputum in patients with chronic bronchitis and emphysema whose clinical, radiologic and functional status were simultaneously defined. Patients were referred principally from the chest clinic of the Albany Hospital and were subsequently admitted to the hospital for investigation. A few patients admitted with acute exacerbations of bronchitis or with asthma were also included in the study. The effect of treatment with penicillin or broad-spectrum antibiotics on the quantity and bacterial flora of the sputum was also studied.

METHODS

Clinical studies included electrocardiography, chest radiology, pulmonary function tests and estimation of the oxygen and carbon dioxide content and oxygen capacity of the arterial blood before and after a short period of exercise by stepping. The maximum breathing capacity was estimated by collection of expired air in a Douglas Bag through a high-velocity valve. Vital capacity was estimated by maximal expiration into a modified Benedict-Roth spirometer after maximal inspiration. Cournand's formulas[1] were used in order to calculate the predicted normal maximum breathing capacity and vital capacity for each patient. The residual air and total lung volumes were estimated by the open circuit method. The percentage of nitrogen remaining in the expired air after a period of oxygen breathing for seven minutes was taken as the index of pulmonary mixing. Functional data were used to substantiate the clinical and radiologic evidence of emphysema. Bronchoscopic examinations were made on single occasions in twenty of the total twenty-six patients in the study.

Sputum was obtained by collection over a twenty-four-hour period and sometimes also as a single freshly coughed specimen. After at least three days of sputum collection, bronchoscopy was performed under local anesthesia and bronchial secretion was aspirated into a mixture of 50 per cent broth in saline. Nasopharyngeal swabs from the posterior nasopharynx and ordinary pharyngeal swabs were also taken from many of the patients and examined after preliminary incubation in rabbit blood glucose broth (Avery tube) and by ordinary cultivation. Sputum was homogenized as completely as possible by shaking in a paint-mixing machine. Sputums, swabs and the centrifuged deposits from the bronchial specimens after preliminary homogenization were cultivated on blood agar

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and coagulated blood agar plates, aerobically and also anaerobically. Five to 10 per cent CO_2 was added to the air used for aerobic cultivation. Colonies were picked after twenty-four hours incubation and identified by microscopic, cultural and biochemical study. Microserologic typing was performed on suspected pneumococci. Mice inoculated intraperitoneally with sputum, four- to six-hour blood broth cultures of pharyngeal swabs, or the centrifuged deposit from bronchial aspirates were examined in the usual manner when symptoms appeared or death occurred. Pneumococci, if present, were typed whenever possible by using serums prepared in the Division of Laboratories, New York State Health Department.

CLINICAL MATERIAL

Altogether twenty-six patients were studied in varying degrees of completeness. Table I summarizes the clinical diagnosis, pulmonary function tests and details of the arterial blood gases in the twenty patients considered to have chronic bronchitis or bronchiectasis and emphysema. The patients are divided into three groups according to the bacteriologic results with the bronchoscopic specimens. Group A comprised those with and Group B those without pathogenic bacteria in the bronchoscopic specimens. The four patients in Group C were not submitted to bronchoscopy. All but four of all these patients were admitted to the hospital primarily for investigation in a state of chronic illness and were studied without delay. V. S. and W. M. in Group A, A. G. in Group B and T. B. in Group C were admitted because of acute respiratory distress and functional studies were delayed until the acute stage of illness had passed.

The existence of a chronic productive cough was believed to support the diagnosis of bronchitis or of bronchiectasis, but either no sputum or insignificant amounts of sputum were raised by two patients (V. S. and J. D.) whose clinical state otherwise did not differ from that in the others. Bronchiectasis was demonstrated bronchographically in one patient (W. M.) and, though suspected clinically in a second patient (F. T.), the bronchogram showed only minor abnormalities. A cavity was demonstrated radiologically at the right lung apex in one patient (E. McC.) whose sputum contained tubercle bacilli but this patient also showed evidence of gross emphysema. Radiologic evidence of healed pulmonary tuberculosis was demonstrated in one patient (W. A.) whose sputum showed no acid-fast bacilli. Tubercle bacilli were found on two occasions in the sputum of a third patient (J. S.) who exhibited no other evidence on clinical or radiologic grounds of active tuberculosis but who had gross emphysema. Mild essential hypertension without cardiac enlargement was found in one patient (J. A.). A second (J. C.) showed moderate hypertension with left ventricular enlargement. A third patient (J. H.) exhibited hypertension, left ventricular enlargement and also showed evidence of alcoholism and hepatomegaly. Two patients (F. T. and W. M.) had electrocardiographic evidence of right ventricular hypertrophy or strain and had been under outpatient supervision as cases of chronic cor pulmonale. Neither was in a state of congestive failure at the time of admission nor were diuretics needed to keep them free from edema. The electrocardiograms in two more patients (E. McC. and A. G.) showed P waves of P pulmonale type but no other cardiac abnormalities were demonstrable. Emphysema was diagnosed on clinical and radiologic grounds in all of the patients though in three in Group B (J. C., C. K. and W. K.) the findings were considered doubtful. These patients were also the three men whose ventilatory functions were the least impaired and in whom the residual air was less than 50 per cent but more than 45 per cent of the total lung volume. The pulmonary function tests indicated emphysema in varying degree in each of the other seventeen patients. Many patients also exhibited a reduction in the saturation of the arterial blood with oxygen and four showed hypercapnia but none achieved the deviation in the blood gases to be expected in chronic cor pulmonale according to Platts.[6] In all those patients in whom exercise studies were made, a fall in the arterial CO_2 and a slight fall in the oxygen saturation of the arterial blood occurred on exercise, but in only one patient (W. M.) was the change as great as a 10 per cent reduction.

In general, the patients in Groups A, B and C exhibited considerable similarity both in duration of symptoms and in the pattern of clinical findings; and although there were more patients in Group B who were less severely disabled than those in the other groups, there were three patients in Group B who were totally incapacitated (W. T., A. G. and J. S.).

Table II summarizes the findings in six patients with asthma, five of whom were admitted

TABLE I

CLINICAL AND FUNCTIONAL DATA IN CASES OF CHRONIC BRONCHITIS AND EMPHYSEMA

Patient	Age	Clinical Diagnosis (Other Than Chronic Bronchitis)	Duration Pulmonary Symptoms (yr.)	Arterial Oxygen		Arterial CO_2 (Vol. %)	M.B.C.		V.C.		Residual Air (L.)	Total Lung Vol.	R.A./T.L.V. %	Index Pulmonary Mixing (% N_2)
				Content (vols. %)	Saturation (%)		(L./min.)	Per cent of Predicted	(L.)	Per cent of Predicted				
Group A (Bronchoscopic Specimen Containing Pathogenic Organisms—Eight Cases)														
J. H.	51	Emphysema; hypertension; hepatomegaly (alcoholism)	4	19.4	90.6	41.6	49	41	2.66	67	3.66	6.32	58	3.2
E. McC.	59	Emphysema; right apical T.B.	35	16.4	84.1	61.28	32	34	2.9	76	4.74	7.64	62	6.25
F. T.	57	Emphysema; right ventricular hypertrophy; doubtful bronchiectasis	16	16.4	90.0	58.7	47	47	2.6	72	4.73	7.33	65	4.72
F. W.	57	Emphysema	35	15.83	81.8	60.55	28.6	29	2.2	61	4.93	7.13	69	6.11
G. D.	62	Emphysema	20	17.2	90.0	57	34	33	2.53	74	5.78	8.31	69	3.59
V. S.	49	Emphysema	18	21.7	86.8	57.6	26	27	1.84	48	4.37	6.21	70	8.49
L. St. M.	53	Emphysema	4	18.57	90.1	50.23	31.7	33	1.86	47	5.07	6.93	73	4.01
W. M.	47	Bronchiectasis; emphysema; right ventricular strain	25	15.9	81.1	71.0	24	26	0.87	24	3.3	4.17	79	6.72
Group B (Bronchoscopic Specimen Without Pathogenic Organisms—Eight Cases)														
J. C.	46	Chronic bronchitis; hypertension	5	16.9	91.2	47.83	99	88	3.5	91	3.09	6.59	47	2.64
C. K.	61	Chronic bronchitis	35	19.3	96	51.25	74	67	4.11	104	3.87	7.98	48.5	2.27
W. K.	56	Chronic bronchitis	17	18.57	89.5	48.87	75	71	3.68	94	3.58	7.26	49	2.91
W. A.	56	Inactive pulmonary T.B.; emphysema	30	17.0	96.0	53.2	60	67	2.88	80	4.19	7.07	59	4.37
W. T.	65	Emphysema	25	17.0	90.3	49.5	49	58	2.30	73	3.85	6.13	63	2.0
J. A.	55	Emphysema; hypertension	2½	18.44	91.9	45.67	58	56	2.28	62	4.16	6.44	65	2.69
A. G.	59	Emphysema	5	15.4	91.6	61.0	21	24	2.46	72	6.26	8.72	72	5.82
J. S.	66	Emphysema; pulmonary T.B.	10	16.7	97.0	58.1	29	37	1.09	31	4.65	5.74	81	4.76
Group C (No Bronchoscopy Performed—Four Cases)														
P. H.	56	Emphysema	26	17.1	93.5	47.6	34	31	2.38	65	2.69	5.07	53	2.06
C. F.	44	Emphysema	11	18.4	88.8	53.4	44	33	3.13	74	5.82	8.85	65	5.66
T. B.	63	Emphysema; prostatic hypertrophy	7	13.9	88.2	53.2	29.4	31	2.85	81	6.28	9.13	69	5.21
J. D.	48	Emphysema	18	17.85	92.0	54.25	18.7	18	1.37	32	5.33	6.7	79	5.94

in acute respiratory distress. All patients had a productive cough, four were submitted to bronchoscopy and sputums were cultivated in each instance; pulmonary function tests were not performed. The bacteriologic results from these patients were so strikingly negative compared with those from the other patients that they are included for the sake of contrast.

TABLE II

DATA IN CASES OF ASTHMA

Patient	Age	Sex	Clinical Diagnosis	Duration Pulmonary Symptoms (yr.)	Average Daily Weight of Sputum (gm.)	Specimens of Sputum (no.)	Period of Collection of Specimen (days)	Sputum Bacteriology		Bronchial Aspiration
								Pneumococci	H. influenzae	
E. J. C.	67	M	Asthma; acute bronchitis	37	50	6	3	0	1	No pathogenic bacteria
A. M.	36	F	Asthma	3	?	2	1	0	0	No pathogenic bacteria
A. M.	61	F	Asthma: acute bronchitis	9	?	3	3	0	0	None
M. P.	58	F	Asthma; hypertension; coronary heart disease; acute respiratory infection	2	30	4	7	1	0	None
M. S.	45	F	Asthma; antral sinusitis	11	44	5	8	0	3	No pathogenic bacteria
E. H.	53	F	Asthma; acute bronchitis	2	43	1	1	0	0	No pathogenic bacteria
			Totals:			21		1	4	

BACTERIOLOGIC FINDINGS

Tables III and IV give the detailed results of the bacteriologic studies on the patients with chronic bronchitis or bronchiectasis and emphysema. In view of the ubiquity of organisms of the neisseria group, non-hemolytic and green streptococci in sputums, swabs and bronchoscopic specimens the findings regarding these are omitted. It is obvious that strains of the pneumococcus, H. influenzae and Hemophilus parainfluenzae occur with great frequency in the sputums from these patients. The results of bacteriologic examination of bronchoscopy specimens indicate that in some patients the flora was the same as that of the sputum, but that in eight of sixteen patients whose sputum contained pneumococci or H. influenzae, no similar organisms were found by bronchoscopy. The nasopharyngeal swabs did not yield pathogenic bacteria with the same degree of frequency as did the sputum. In two instances a different strain of pneumococcus was present in the nasopharynx from that present in the sputum, and in three instances the same strains were present in both locations. Hemolytic streptococci and Staphylococcus aureus were infrequently recovered from either sputum or bronchoscopic specimens.

EFFECT OF TREATMENT

The small number of observations permit only a general statement. Seven of eight patients whose sputums yielded pneumococci before treatment failed to yield these organisms after a course of intramuscular penicillin for five or six days, but the sixth patient still yielded pneumococci of the same type as before treatment. H. influenzae, if present before treatment, was also recovered from the sputum after penicillin therapy. Chloramphenicol reduced the content of H. influenzae in the sputum but failed to eliminate this organism entirely. Pneumococci were still present in the sputum after treatment with chloramphenicol in two instances and after terramycin® in one instance. The quantity of sputum which was frequently slightly diminished during therapy remained less than that produced before treatment only if the latter was considerable in amount. Patients producing only a small quantity of sputum before treatment usually continue to produce the same amount after treatment. Sufficient data were not available to evaluate the question of correlation between quantity of sputum and the character of the organisms present in the sputum nor were observations made specifically on the question of the purulent nature of the sputum. If the sputum was purulent before treatment, it frequently became white during the course of antibiotics.

COMMENTS

In a previous paper[7] one of us (C. H. S.-H.) discussed the significance of the bacteria of a potentially pathogenic character found in the sputum of patients with chronic bronchitis.

The view was formulated that a state of chronic colonization of the lower respiratory tract exists in chronic bronchitis perhaps as a result of a failure of defense against invasion by nasopharyngeal organisms. The present investigation was planned in order to establish, if possible, the origin of the various organisms recovered in the sputum in patients whose clinical and physiologic status was defined. The mere presence of bacteria in the sputum can be explained by contamination of the sputum by nasopharyngeal secretions or saliva as well as by origin from organisms located in the bronchi or bronchioles. Moreover, the bacterial species found in the sputum in cases of chronic bronchitis are similar to those found in the nasopharynx in normal individuals.

The bacteriologic data obtained by the study of bronchoscopic specimens appear to establish an origin of the pneumococci and other organisms from the lower respiratory tract in half of the patients studied. The absence of pathogenic bacteria in the bronchoscopic specimens from the remaining patients could be explained

TABLE III

BACTERIOLOGIC FINDINGS IN THE SPUTUM OF CASES OF CHRONIC BRONCHITIS AND EMPHYSEMA

Patient	Average Daily Weight of Sputum (gm.)	Specimens Examined (no.)	Period of Collection of Specimens (days)	Pneumococci	H. influenzae*	Hemolytic streptococci	Staph. aureus	Coliform bacilli	Tubercle bacilli
			Group A						
J. H.	23	8	8	2	1	1	0	7	0
E. McC.	131	5	9	5	4	0	0	0	3
F. T.	195	3	3	3	3	0	0	0	0
F. W.	?	5	14	5	2	0	0	3	0
G. D.	8	3	5	3	1	3	0	0	0
V. S.	Nil	1	4	1	0	0	0	0	..
L. St. M.	72	5	9	5	5	0	0	0	0
W. M.	125	7	7	7	6	0	1	0	0
			Group B						
J. C.	13	4	4	0	4	0	0	0	0
C. K.	?	3	12	1	0	0	0	0	0
W. K.	109	5	13	5	0	1	0	0	0
W. A.	?	3	12	2	3	0	0	1	0
W. T.	54	7	3	2	2	0	0	0	0
J. A.	?	4	8	4	3	0	0	0	0
A. G.	?	5	15	3	2	0	0	0	0
J. S.	7	6	8	5	0	0	0	0	2
			Group C						
P. H.	14	5	5	4	4	0	1	0	1
C. F.	?	1	1	1	0	0	0	0	0
T. B.	?	3	5	3	2	0	0	1	0
J. D.	Nil	0	0	0	0	0	0	0	0
Totals:		83		61	42	5	2	12	6
			Percentage	73.5	50.6	6.0	2.4	14.4	7.2

* Includes H. para-influenzae.

either on the basis of clinical differences or because of the fact that the specimens were in some way unsatisfactory. The clinical and functional data, although indicative of quantitative differences between the two groups of patients (those with and those without pathogenic bacchial tree, and that single bronchoscopic specimens may fail to be representative of secretions from all areas. In any case, the data obtained from nasopharyngeal swabs did not support the view that the organisms in the sputum were derived from nasopharyngeal secretion by a

TABLE IV

COMPARISON OF SPUTUM, BRONCHOSCOPIC ASPIRATION AND NASOPHARYNGEAL FLORA

Patient	Sputum	Bronchoscopic Aspiration	Nasopharynx
		Group A	
J. H.	Pneumococcus (untyped); H. para-influenzae; anaerogenic coliform	Pneumococcus (untyped); anaerogenic coliform	.....
E. McC.	Pneumococcus 17; H. influenzae	Pneumococcus 17	Pneumococcus (untyped)
F. T.	Pneumococcus 17; H. influenzae	H. influenzae	.....
F. W.	Pneumococcus (untyped) Pneumococcus 23; H. para-influenzae	Pneumococcus (untyped); H. influenzae	H. para-influenzae
G. D.	Pneumococcus 19; hemolytic streptococcus	Pneumococcus 19; hemolytic streptococcus; Staph. aureus	Pneumococcus 3; pneumococcus 19; hemolytic streptococcus
V. S.	Pneumococcus 20; pneumococcus 24; pneumococcus 33	Pneumococcus 33	No pathogenic organisms
L. St. M.	Pneumococcus 3; H. influenzae	H. influenzae	No pathogenic organisms
W. M.	Pneumococcus 23; pneumococcus 3; H. influenzae	Pneumococcus 23; H. influenzae	.....
		Group B	
J. C.	H. influenzae		No pathogenic organisms
C. K.	Pneumococcus (untyped)		No pathogenic organisms
W. K.	Pneumococcus 18		Pneumococcus 18
W. A.	Pneumococcus 8; pneumococcus (untyped)		No pathogenic organisms
W. T.	Pneumococcus 10A; H. influenzae	No pathogenic organisms in Group B	No pathogenic organisms
J. A.	Pneumococcus 11; H. influenzae		No pathogenic organisms
A. G.	Pneumococcus 9; H. para-influenzae		Pneumococcus 9; H. para-influenzae
J. S.	Pneumococcus 10A		No pathogenic organisms

teria in the bronchoscopic specimens), failed to establish qualitative differences. It seems important that the bronchoscopic specimens were sometimes obtained with difficulties of a technical character because of the degree of dyspnea of the patients and were in any case single collections of material. May[4] has stressed the inhomogeneous character of the sputum in cases of chronic bronchitis and the bronchoscopic specimen is derived simply from that material found in the larger bronchi at the time of examination. It is conceivable, therefore, that the organisms found in the sputum after a prolonged period of collection are derived from various parts of the bronprocess of mechanical contamination. Data obtained by a long-continued period of observation on the sputum and nasopharyngeal swabs of cases of chronic bronchitis in England[3] support this latter conclusion. Over a prolonged period (nineteen months), among ninety-five sputum samples obtained from thirteen subjects seventy-five (79 per cent) yielded pneumococci. The nasopharyngeal carrier rate of pneumococci in these subjects was 45 per cent of ninety-seven specimens.

The present data, although confirming the significance of pathogenic bacteria in relation to the state of chronic bronchitis, do not sug-

gest the means whereby the state is established. The absence of similar organisms from the sputum in patients with asthma is important if confirmed in a larger series of patients. Mechanical changes in the lower respiratory tract in patients with chronic bronchitis may be important in relation to the persistence of the bacterial infection.

SUMMARY

1. This study was an effort to obtain data concerning the origin of bacteria in the sputum of patients with chronic bronchitis and emphysema. Of the sixteen patients who were bronchoscoped, eight had similar pathogenic flora in the sputum and bronchial aspirate. The remaining eight had pathogenic bacteria in the sputum but not in the bronchial aspirate. Possible reasons for this difference are discussed.

2. The data presented do not support the view that organisms in the sputum are derived from the nasopharynx during the process of expectoration.

3. The low incidence of pathogenic bacteria in the sputum of patients with bronchial asthma is important if confirmed in a larger series.

Acknowledgments: The patients on whom these investigations were made were under the care of Dr. R. T. Beebe and Dr. F. M. Woolsey, Chiefs of the respective Departments of Medicine of the Albany Hospital and the Veterans Hospital, Albany, to whom our thanks are due. The laboratory investigations were made partly in the Cardiopulmoanry Function Laboratory of the Albany Hospital and partly in the Division of Laboratories and Research of the New York State Department of Health, Albany. We wish to thank Dr. V. Tomkins, Head of the Diagnostic Section of the State Laboratory and Dr. W. R. Thompson for arranging for provision of laboratory facilities for the studies.

We are indebted to Dr. R. J. Erickson of the Albany Hospital and Dr. J. H. Cullen of the Veterans Hospital, Albany, who kindly referred patients for investigation. Dr. E. A. Kopp of the Veterans Hospital, Albany, carried out bronchoscopic examinations on some of the patients.

This investigation could not have been made without the active encouragement and support of Dr. Gilbert Dalldorf, Director of the New York State Laboratory, who also made it possible for one of us (C. H. S.-H.) to visit Albany in order to arrange a program of clinical research.

We are indebted also to the Sterling-Winthrop Research Institute for financial assistance.

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Pulmonary Arterial Hypertension with Markedly Increased Pulmonary Resistance*

The Pulmonary Vascular Obstruction Syndrome

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THE pulmonary arterial pressures of normal individuals are low, approximately one-fourth to one-fifth of systemic pressures.[1] The mean pressure gradient across the pulmonary vascular bed is, according to Poiseuille's law, a product of the resistance in the pulmonary arteriolar system and the pulmonary blood flow. Pulmonary arterial hypertension thus could be the result of either an increase in pulmonary blood flow with relatively normal resistance or, conversely, of an augmented pulmonary vascular resistance with relatively normal or even diminished pulmonary blood flow. Clinical examples of both these situations have been reported frequently. Pulmonary arterial hypertension with increased pulmonary blood flow has commonly been found in patients with large ventricular septal defect or patent ductus arteriosus.[2,3] Chronic cor pulmonale with normal or decreased flow and markedly increased pulmonary arteriolar resistance has also been described repeatedly.[4] In our experience, the majority of patients with pulmonary hypertension occupy an intermediate position between these two extremes representing cases with cardiac shunt and a moderately increased pulmonary flow and resistance.

This paper presents a group of seven patients with maximal increase in pulmonary vascular resistance, who comprise a clinically homogeneous group. In addition to the pulmonary vascular obstruction some of these patients had congenital cardiac defects. In others the presence or absence of such defects could not be demonstrated. The purpose of this paper is to call attention to the clinical and physiologic characteristics of this pulmonary vascular obstruction syndrome, to outline the problems in differential diagnosis and to emphasize its occurrence in patients with or without congenital heart disease.

MATERIAL AND METHODS

Six of our patients were studied at the Children's Medical Center of Boston, and a seventh was hospitalized at the Massachusetts General Hospital[5] and examined there by one of us. In addition to the routine laboratory studies, radiologic and electrocardiographic examinations were performed in all patients. Results of cardiac catheterization are available in five patients, and autopsy information was obtained in the other two. One patient was studied by angiocardiography.

Clinical Features (*Table* 1)

History and Physical Examination. Seven patients ranging between the ages of nine and thirty-five years were studied. All were females with reasonably good growth and development. Cyanosis was present in six cases; it had been noted at birth in three instances and at ages two, five and seven years, respectively, in the other three patients. The seventh individual (C. K.)

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was not noted to be cyanotic in spite of definite arterial unsaturation. Exercise intolerance of varying degrees was noted in all, though evidence of congestive failure was lacking. A history of syncope, hemoptysis and precordial pain on exertion was elicited in some of our patients.

Definite clubbing of the fingers was noted in all of our cyanotic patients. Chest deformity was not observed in any instance. The cardiac impulse was relatively quiet, and was maximal over the xiphoid process. Thrills were uniformly absent. The most constant and obvious auscultatory finding was a very loud, normally split and often palpable pulmonic second sound. Two patients had no murmurs; a systolic murmur, grade 2-3 in intensity, was present at the apex or the second-fourth left interspace in the remaining five patients. The murmur was blowing in

TABLE I

CLINICAL FEATURES

Case No. and Patient's Initials	Sex	Age at Study	Development	Murmur First Noted (yr.)	Cyanosis First Noted (yr.)	Exercise Intolerance	Syncope	Precordial Pain	Hemoptysis	Clubbing	Intensity of 2nd Pulmonic Sound	Heart: Murmurs: Systolic: Location	Heart: Murmurs: Systolic: Grade	Heart: Murmurs: Diastolic: Location	Heart: Murmurs: Diastolic: Grade	Radiologic: Right Ventricle	Radiologic: Cardiomegaly	Radiologic: Pulmonary Artery: Main Segment—Size	Radiologic: Pulmonary Artery: Main Segment—Pulsations	Radiologic: Pulmonary Artery: Hilar Dance	Radiologic: Pulmonary Artery: Peripheral Pulmonary Vessels	ECG: Ventricular Hypertrophy	ECG: Height of R in Lead V_1 (mm.)	ECG: IRBBB***	ECG: P-pulmonale
I. C.K.	F	9	F××	8	0	+	0	0	0	0	+++	II Lis.	II	II Lis.	II	+	0	+	+	+	N⁰	R* L**	22	0	0
II. M.L.	F	15	G×××	1	2	+	0	0	+	+	+++	Apex	III	0	0	+	±	N⁰	N⁰	0	N⁰	R*	12	0	0
III. M.R.	F	11	F××	9	B×	+	0	0	0	+	+++	IV Lis.	II	0	0	+	0	+	+	+	N⁰	R*	9	+	+
IV. B.H.	F	24	F××	0	B×	++	0	+	+	+	+++	III Lis.	III	0	0	+	0	+	N⁰	0	D⁰⁰	R*	B	+	0
V. J.Z.	F	35	G×××	0	B×	++	+	+	+	+	++	0	0	0	0	+	0	+	N⁰	0	N⁰	R*	9	+	0
VI. J.C.	F	15	G×××	0	7	++	++	0	0	+	++	0	0	0	0	+	0	+	N⁰	0	N⁰	R*	?	0	0
VII. S.H.	F	19	F××	5	5	++	+	+	+	+	++	IV Lis.	III	II Lis.	II	+	0	+	+	+	D⁰⁰	R*	16	+	+

× birth
×× fair
××× good

0 normal
00 diminished

*R—right
**L—left
***—incomplete right bundle branch block

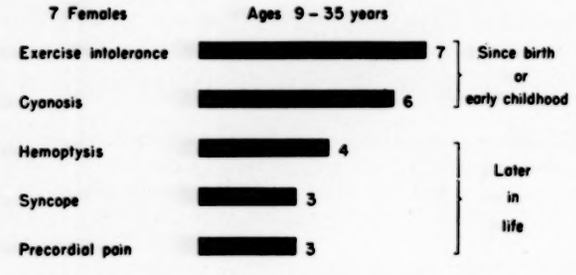


FIG. 1. Patients and their symptoms.

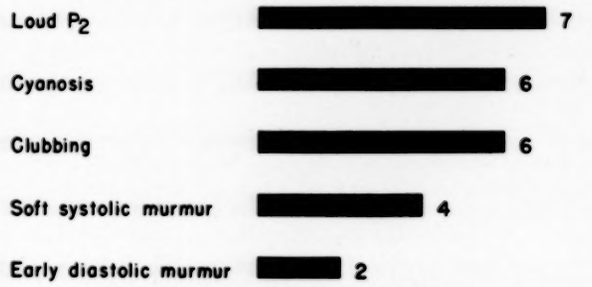


FIG. 2. Summary of physical findings.

3A 3B 3C

FIG. 3. Radiogram of patient B. H. A, postero-anterior view; B, right anterior oblique view; C, left anterior oblique view.

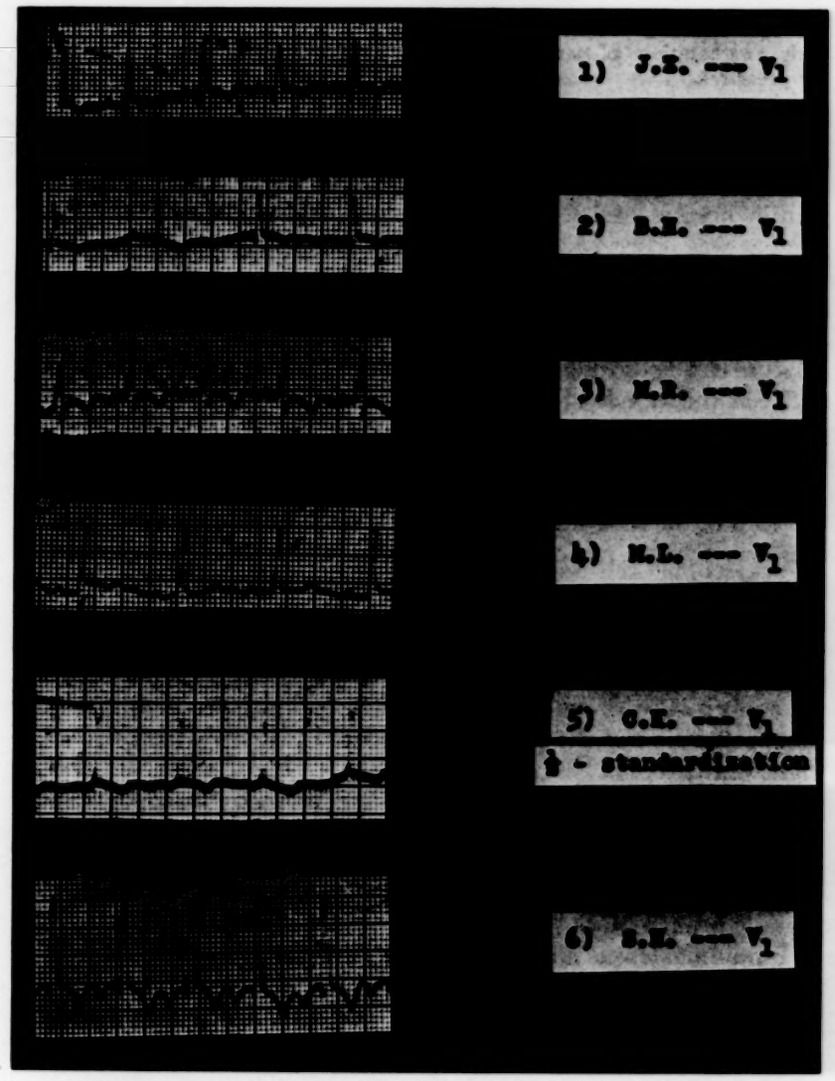


FIG. 4. Right precordial electrocardiograms: lead V_1 in six cases of pulmonary vascular obstruction syndrome.

character and was not transmitted well to the neck or the back. No mid-diastolic murmur was noted in this group but two patients had a grade 2 early diastolic blow at the second left interspace. (Figs. 1 and 2.)

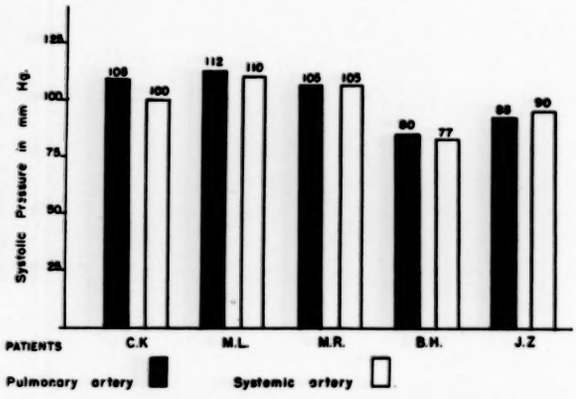


FIG. 5. Graphic presentation of pulmonary and systemic systolic pressures.

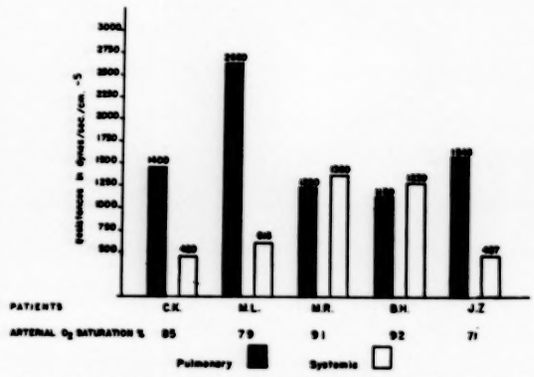


FIG. 6. Comparison of pulmonary and systemic resistances in relation to arterial saturation.

Radiologic Examination. Right ventricular enlargement was noted in the left anterior oblique view in all patients. The cardio-thoracic ratio was, however, within normal limits in all. No auricular enlargement was observed. The main pulmonary artery segment in the antero-posterior view was of normal or increased size and showed normal or increased pulsations. The pulmonary vasculature characteristically showed a discrepancy between the vessels of the hilum and the periphery; the hilar markings were exaggerated, occasionally even showing hilar "dance," whereas the vascular markings in the middle and outer third of the lung fields seemed normal or diminished. Typical radiograms are shown in Figure 3A, B and C.

The angiocardiographic examination performed in patient, M. R., demonstrated a normal right atrium, right ventricle and pulmonary artery. The only abnormality revealed by this examination was opacification of the ascending aorta from the right ventricle.

The Electrocardiogram. Right ventricular hypertrophy was apparent in the unipolar chest leads of all patients. (Fig. 4.) Additional left ventricular hypertrophy was seen in one. Incomplete right bundle branch block was present in four instances. P-pulmonale was noted in only two cases.

Cardiac Catheterization Studies

Right heart catheterization was performed in six of our seven patients. The data obtained and the calculations in five cases are presented in Table II. It should be mentioned, however, that the calculations were based on the assumption that the pulmonary venous blood was fully saturated. As we will point out later in the discussion, such an assumption is not necessarily correct in all instances.

The pulmonary arterial systolic pressure was practically identical with the systemic arterial pressure in all patients. (Fig. 5.) It is quite evident from Table II that this resulted from the very high pulmonary vascular resistance, which was found to be five to twelve times as high as the upper normal values; in three instances pulmonary resistance was even higher than the systemic arterial resistance. Arterial unsaturation of varying severity was present in all patients; the correlation between the degree of arterial unsaturation and the ratio of pulmonary to systemic resistance is presented in Figure 6. Right-to-left shunts of varying magnitudes were calculated in all. The site of the shunt was assumed to be at the ventricular level in the three patients in whom a simultaneous left-to-right shunt through a ventricular defect could also be demonstrated. Further evidence, supporting the presence of a ventricular defect in one of these three patients, was obtained by angiocardiography. The origin of the arterial unsaturation was not clearly demonstrated in our remaining two catheterized patients.

Postmortem Material

Autopsy examination was performed in two patients. No valid catheterization data were available in either of these cases. Nevertheless, it was considered appropriate to include them in this series of patients with pulmonary vascular

TABLE II
PHYSIOLOGIC DATA

Case No. and Patient's Initials	Body Surface Area (m^2)	Pressures (mm. Hg)					Oxygen Consumption (cc./min.)	Oxygen Content (vol. %)							Cardiac Index (L./min./m^2)			Shunt Index (L./min./m^2)			Resistances (dynes-sec-cm^{-5})	
		Pulmonary Artery (syst./diast.)	Pulmonary Artery (mean)	Right Ventricle (syst./diast.)	Right Auricle (mean)	Brachial Artery (syst./diast.)		Pulmonary Artery	Right Ventricle	Right Auricle	Superior Vena Cava	Brachial Artery	Oxygen Capacity	Systemic Arterial Saturation (%)	Systemic Index	Pulmonary Index	Effective Pulmonary Index	Shunt—Total Right-to-left, Index	Shunt—Total Left-to-right, Index	Net Shunt, Index	Systemic Resistance	Pulmonary Resistance
I. C. K.	1.1	108/75	88	108/8	7	100/60	175	14.7	14.2	14.9	14.4	16.1	18.7	85	9.5	3.8	3.8	5.7	0	5.7	420	1400
II. M. L.	1.4	112/75	90	112/3	4	110/72	175	16.7	16.0	17.1	16.6	19.5	24.5	79	4.3	1.8	1.8	2.5	0	2.5	616	2660
III. M. R.	1.1	105/65	76	105/8	9	105/80	180	12.7	12.0	11.0	11.2	17.1	18.5	91	3.4	3.8	2.7	0.5	0.9	0.4	1360	1220
IV. B. H.	1.4	80/49	61	77/4	3	77/46	161	15.1	14.1	12.0	11.5	18.6	19.9	92	1.6	2.8	1.5	0.1	1.3	1.2	1230	1150
V. J. Z.	1.6	88/65	72	?	8	90/70	199	15.7	?	14.8	?	17.0	23.5	71	5.7	1.7	1.5	4.2	0.2	4.0	457	1540

obstruction syndrome on account of the severe pulmonary vascular changes found at the postmortem examination. It is interesting to point out that Case VI (J. C.) at autopsy showed an aortopulmonic fenestration, whereas only a probe-patent foramen ovale was present in Case VII (S. H.). In spite of this basic discrepancy between the two hearts, the pulmonary vascular changes were quite similar, consisting of intimal and medial proliferation with old and recent thrombotic phenomena. As pointed out before, the clinical pictures of the two patients were also quite similar.

Patient J. C. (Case VI) died within a few minutes after performance of a decholin circulation time. The pertinent portions of the autopsy protocol are as follows:

"Heart weighs 270 gm. The right ventricle is greatly dilated and hypertrophied. The wall is 14 mm. thick, the same as the left ventricle. The foramen ovale is closed. One cm. distal to both the pulmonary and aortic valves there is a communication 12 mm. in diameter between the pulmonary artery and the aorta. (Fig. 7.)

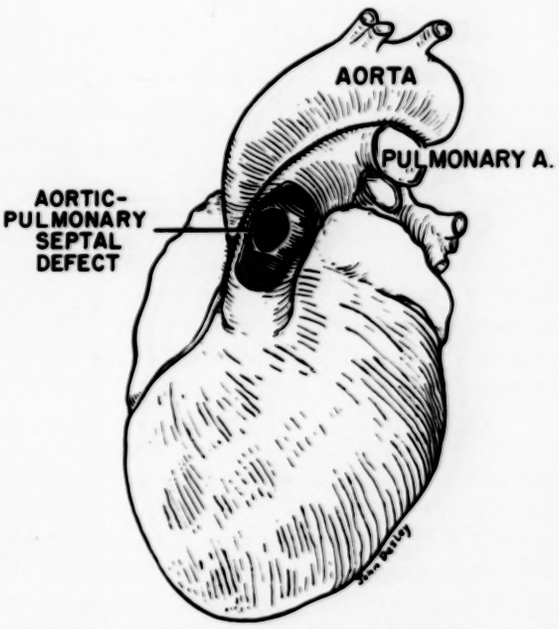
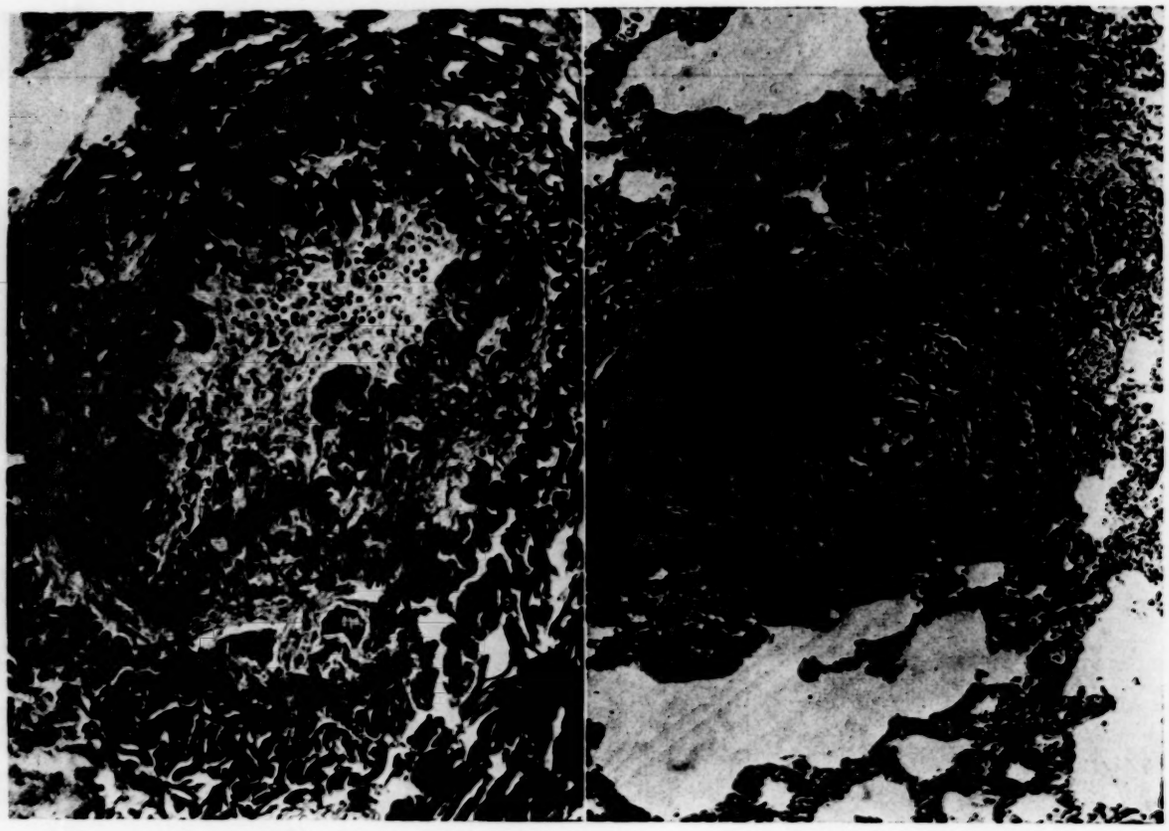


FIG. 7. Schematic presentation of autopsy findings in Case. VI.*

* Figures 7 to 9 are reproduced from *New England J. Med.*, 249, 336–338, 1953.



8 9

FIG. 8. Microscopic picture of pulmonary vasculature in Case VI. Small artery (300 μ) with giant cells adjacent to the internal elastic lamina and deep in the media. The lumen is filled with loose connective tissue and scattered inflammatory cells.

FIG. 9. Microscopic picture of pulmonary vasculature in Case VI. Recanalized thrombus with multiple lumen in a small artery (300 μ).

This opening is circular and has a smooth margin. The ductus is closed. Just distal to this fenestration the pulmonary artery is 9 cm. in circumference and the aorta is 7 cm.

"The lungs weigh 560 gm. There is a grey nodule with recent hemorrhage situated in the right middle lobe. There are rather large peripheral branches of the pulmonary artery which attain a size of 0.5 cm. in diameter near the pleural surface.

"Microscopically, the pulmonary arteries and the arterioles show considerable intimal thickening and in many of them the lumen is completely occluded by loose fibrous tissue. (Fig. 8.) In others, a small lumen is still in evidence. In a few arterioles organization appears to be taking place in a thrombus, because there are several lumina still present in this material. (Fig. 9.) Some of these partially organized thrombi contain multinucleated giant cells, the nuclei of which are placed peripherally. The main pulmonary artery demonstrates increased thickness of the medial wall with marked increase in the amount of elastic tissue, so that it resembles the aorta."

Patient S. H. (Case VII) died during cardiac catheterization. The pertinent data obtained from the autopsy protocol are as follows:

"Combined weight of heart and lungs: 700 gm. Heart: Right ventricular wall 2 cm., left ventricular wall 1.2 cm. in thickness. There is enormous right ventricular hypertrophy. The ductus arteriosus is a fibrous cord. The foramen ovale consists of a small slit-like opening measuring 1 cm. in length and 1 mm. in width. The pulmonary outflow tract is moderately distended. There are no other gross cardiac findings of note.

"The intrapulmonary branches of the pulmonary artery are relatively narrower than normal. Throughout the pulmonary artery and its branches, patchily distributed athero-

matosis is seen grossly, however, without parietal thrombosis or ulceration. No emboli are evident.

"Microscopically, the large elastic pulmonary branches show mostly an atheromatous change varying in degree from small discrete collections of subendothelial cells to large patches. (Fig. 10.) The media is mostly hyperplastic with duplication of elastic membranes and slight degenerative changes. Only occasionally, thrombosis with recanalization is seen in the elastic arteries.

"The muscular pulmonary arteries are the seat of a marked subendothelial fibrosis that occludes the lumen. Many are obliterated by thrombi, some of which show recanalization.

"Many but not all the arterioles show an increase of collagen in their media and intima so as to reduce their lumina. Sometimes the diameter of the lumen equals the thickness of the wall. Capillaries and veins are normal."

FIG. 10. Microscopic picture of pulmonary vasculature in Case VII. Photomicrograph of a muscular artery showing an obliterative proliferative endarteritis; × 125.

CASE REPORTS

CASE I. C. K., a nine and one-half year old white girl, had always been well except for a forceful heart beat first noted by her parents at three months of age. There was no dyspnea but she appeared to tire more easily than her friends. Prior to a planned tonsillectomy one year ago, a murmur was detected and she was referred to this clinic for evaluation. There had been no obvious cyanosis, squatting or spells.

Physical examination showed a well nourished and well developed girl in no distress. Pulse rate was 95, blood pressure, 100/70. There was no definite evidence of cyanosis and no clubbing was present. The second sound was accentuated along the upper left sternal border. In this same area there was a grade II systolic and a soft blowing early diastolic murmur. There were no other findings of note.

Laboratory data were as follows: hemoglobin, 13 gm. per cent; red blood cells, 3.79 million; fluorescein circulation time (arm to tongue), eleven seconds.

X-ray examination showed a normal sized heart with a prominent pulmonary artery segment. There was some suggestion of selective right ventricular enlargement. The peripheral pulmonary vasculature was not remarkable. Cardiac catheterization revealed identical pressures in the pulmonary artery, right ventricle and brachial artery. There was no evidence to indicate a left-to-right shunt but the arterial oxygen saturation indicated the probability of a right-to-left shunt, although the site at which this occurred could only be conjectured. There was no clinical evidence to suspect parenchymal pulmonary disease. The pulmonary blood flow was normal but the pulmonary vascular resistance was markedly increased (seven times the normal value).

CASE II. M. L., a fifteen year old white female, was first noted to have a heart murmur at the age of ten months. Minimal cyanosis and exercise intolerance were observed first at the age of two years. The exercise intolerance was never striking but she did become dyspneic on running. There was no orthopnea, nocturnal paroxysmal dyspnea or ankle edema. On two occasions in the past three years she had moderate hemoptysis each lasting about two days.

Physical examination revealed a well developed and well nourished girl who appeared comfortable. Pulse rate was 80, blood pressure, 120/70. She was mildly cyanotic with moderate clubbing of the digits. The second sound in the pulmonic area was split, loud and snapping.

There was a grade III blowing systolic murmur at the apex.

X-ray showed the heart to be only slightly enlarged with a normal configuration. The pulmonary vasculature was normal. There was no hilar dance. Electrocardiogram revealed marked right ventricular hypertrophy.

Laboratory data were as follows: hemoglobin 19.4 gm. per cent; red blood cells, 6.47 million; hematocrit 59 per cent.

Cardiac catheterization revealed both right ventricular and pulmonary arterial systolic pressures to be in the systemic ranges. There was no detectable left-to-right shunt; a right-to-left shunt was indicated by the systemic arterial saturation of 79 per cent (the level of the shunt could not be demonstrated by this procedure); the pulmonary vascular resistance was approximately five times the systemic and over twelve times the normal. The pulmonary blood flow was quite small.

It was not believed that any further diagnostic or therapeutic measures were indicated for the time being and she was discharged to the care of her family physician.

CASE III. M. R., an eleven year old white female, was noted to become cyanotic about the mouth and dyspneic on crying, shortly after birth. She was always considered small for her age, required frequent rest periods and was never able to maintain the physical pace of her playmates.

Physical examination revealed a slender but well developed girl in no acute distress. She was moderately cyanotic with minimal clubbing of the fingers. Pulse rate was 100, blood pressure, 120/80. The only positive findings on cardiac examination were the markedly accentuated and narrowly split pulmonic second sound and a grade II precordial systolic murmur.

Laboratory data were as follows: hemoglobin 15 gm. per cent; red blood cells, 6.70 million; hematocrit 50 per cent; fluorescein circulation time (arm-to-lip) fifteen seconds. Electrocardiogram showed right ventricular hypertrophy. Incomplete right bundle branch block was present.

X-ray and fluoroscopy showed the heart to be of normal size with some selective right ventricular enlargement. The pulmonary artery appeared slightly prominent with a suggestion of a hilar dance on the right. The peripheral pulmonary vasculature appeared normal. Cardiac catheterization demonstrated identical systolic pressure levels in the brachial artery, pulmonary artery and the right ventricle. Evidence for a left-to-right shunt through a ventricular defect was obtained by blood sampling for oxygen content. Arterial saturation was 91 per cent and could not be raised to full saturation by administering pure oxygen by mask. The latter finding further increased the evidence for a right-to-left shunt and rendered the possibility of unsaturation on the basis of parenchymal pulmonary disease rather unlikely. The pulmonary vascular resistance was only slightly below the systemic level with the former being about nine times normal. Pulmonary flow was only slightly above normal. Angiocardiography (by demonstrating premature opacification of the aorta) strongly suggested the presence of a ventricular septal defect.

CASE IV. B. H., a twenty-four year old housewife, was allegedly blue at birth but only minimally cyanotic at rest and on exertion since then. No squatting or syncope had been noted. She experienced precordial pain occasionally on exertion. She had moderate dyspnea after climbing two flights of stairs. She complained of some vertigo when tired. She was able to do all but heavy housework. One month prior to admission she had experienced her first hemoptysis following a severe respiratory infection.

Physical examination showed her to be somewhat thin but well developed. Pulse rate was 84, blood pressure 110/75. She had slight clubbing and minimal cyanosis of lips and nail beds. The second pulmonic sound was split and markedly accentuated. There was a grade III systolic murmur in the third left interspace. No diastolic murmurs were heard. There was no venous distention, hepatomegaly or edema.

Laboratory data were as follows: vital capacity, 2,200 cc.; hematocrit, 56 per cent; red blood cells, 5.5 million; circulation time with decholin (arm to tongue) twelve seconds.

X-ray and fluoroscopy revealed the heart to be within normal limits in size and a prominent main pulmonary artery with dilatation extended into the left branch of the main pulmonary artery. The peripheral pulmonary vasculature was definitely diminished. The right ventricle was prominent. Electrocardiogram showed right ventricular hypertrophy and incomplete right bundle branch block. Cardiac catheterization revealed almost identical systolic pressure in the right ventricle, the pulmonary and the brachial

artery. The pulmonary flow, although greater than systemic, was still well within normal limits. The pulmonary and systemic resistances were equal, the former being about seven times normal. The demonstration of a small left-to-right shunt at the ventricular level suggested the presence of a ventricular septal defect. Minimal systemic unsaturation (92.4 per cent) suggested also the existence of a small right-to-left shunt.

Case v. J. Z., a thirty-five year old white female, was noted to be cyanotic at birth. She had had repeated severe respiratory infections in infancy and childhood, with definite exercise intolerance since an early age, with squatting and occasional syncope. In recent months she complained of chest pain on exertion and in cold weather. In the past month she had had several small hemoptyses.

On physical examination she appeared well developed and nourished but with obvious dyspnea on slightest exertion. The blood pressure was 105/80, pulse 102. She was moderately cyanosed and showed marked clubbing. Cardiac examination revealed no chest deformity, a markedly accentuated, narrowly split second pulmonic sound and no murmurs.

X-ray showed a heart size within the lower limits of normal with a moderately enlarged pulmonary artery. The pulmonary vasculature was normal. Electrocardiogram showed right ventricular hypertrophy. The P waves were normal. There was incomplete right bundle branch block.

Laboratory data were as follows: urine normal; hematocrit 73 per cent; sedimentation rate normal; vital capacity 2,200 cc.; decholin circulation time (arm-to-tongue) nine seconds. Cardiac catheterization revealed the following salient data: pulmonary arterial hypertension in the systemic range; diminished pulmonary flow; pulmonary vascular resistance approximately four times the systemic and ten times the normal value with systemic arterial saturation of 77 per cent. It was evident that a right-to-left with negligible left-to-right shunt existed but the site of the shunt could not be designated.

A phlebotomy was done with removal of 1 L. of blood, and the patient was discharged.

Case vi. J. C., a fifteen year old white girl, was admitted to the pediatric service of the Massachusetts General Hospital at five years of age with the presumptive diagnosis of rheumatic fever and was hospitalized for one year. She was noted to be cyanotic and somewhat dyspneic thereafter but these symptoms had become more marked in the past seven months. Syncopal attacks also dated back to five years of age and in recent months had become a daily occurrence. These fainting spells were precipitated by exertion or emotional distress.

Physical examination revealed a well developed and well nourished girl. She showed clubbing of the digits and marked cyanosis of the lips, fingers and toes. Examination of the heart revealed no murmurs. The pulmonic second sound was markedly accentuated. There were no other significant findings.

Laboratory data were as follows: hemoglobin 17.7 gm. per cent; decholin circulation time (arm-to-tongue) seven seconds. The electrocardiogram was consistent with right ventricular hypertrophy.

X-ray and fluoroscopy showed no generalized enlargement of the heart, although the right ventricle seemed somewhat prominent. The main pulmonary artery segment was prominent. No hilar dance was present. The peripheral pulmonary vasculature seemed normal.

This patient suddenly expired while under observation a few minutes after the decholin circulation time was performed. The salient findings at autopsy have been discussed earlier.

Case vii. S. H. At the age of five years this nineteen year old white housewife was first told that she had "heart trouble." Prior to this her mother occasionally noted cyanosis of her hands. At the age of ten years, following mild exertion, she had a syncopal episode. A tendency to nosebleeds manifested itself thereafter. Since the age of thirteen years exertional dyspnea, vertigo, weakness and cyanosis had been progressive.

On physical examination she appeared acutely and chronically ill. There was some pallor, cyanosis was definite, clubbing was present. Dyspnea at rest was evident. A grade iii blowing systolic murmur was present all along the left sternal border, maximally at the fourth left interspace. The pulmonic second sound was markedly accentuated and narrowly split. An early, blowing diastolic murmur was audible at the left sternal border. Blood pressure over the right arm was 130/104 mm. Hg.

Laboratory data were as follows: hemoglobin, 16.4 gm. per cent; red blood cells, 5.45 million; urine examination, negative. The electrocardiogram showed marked right ventricular hypertrophy. Radiologic examination revealed enlargement of the right ventricle and the main

pulmonary arterial segment. Expansile pulsations of the main pulmonary arterial branches were noted by fluoroscopy. The peripheral pulmonary vasculature seemed diminished.

In order to confirm the clinical impression of pulmonary vascular obstruction, cardiac catheterization was performed. The procedure was completed without noticeable difficulty. After removal of the catheter her respiration became gasping and shallow, and despite emergency resuscitation she expired. Analysis of catheterization data revealed a pulmonary arterial pressure of 130/100 mm. Hg as compared with a peripheral artery pressure of 88/65 mm. Hg. Pulmonary vascular resistance was calculated to be 5,280 dynes-sec-cm^{-5} as compared with a systemic vascular resistance of 2,590 dynes-sec-cm^{-5}. These values are not included in the table of physiologic data because of the sudden death of the patient within a few minutes after completion of the procedure. It was believed that the values obtained probably represented a preterminal state.

COMMENTS

The seven patients analyzed in this paper present a fairly uniform clinical and physiologic pattern. They all gave a history of exertional dyspnea; early cyanosis was noted in all but one patient. The only constant cardiac finding on physical examination was the marked accentuation of the second pulmonic sound. X-rays and electrocardiograms revealed right ventricular hypertrophy. The pulmonary vasculature was prominent at the hilum and normal or diminished at the periphery of the lung fields. All the cases showed pulmonary arterial hypertension with increase in pulmonary vascular resistance to at least systemic levels. Arterial unsaturation was present in all.

A clinical picture very similar to the one described has been presented by Dresdale,[4] Wood,[7] Dressler[6] and others as essential pulmonary hypertension. In these cases, as in ours, pulmonary hypertension secondary to parenchymatous pulmonary disease, kyphoscoliosis, syphilis and mitral stenosis was excluded. All patients with congenital heart disease were also excluded from the diagnosis of essential pulmonary hypertension on the assumption that such cases represent different etiologic entities.[8] Such a distinction was certainly not possible in our material on clinical grounds alone. Patients in whom the presence of congenital heart disease was excluded with certainty (S. H.), those in whom the presence of congenital heart disease could not be proven (C. K. and M. L.) and those with proven congenital heart disease (J. C., M. R., B. H. and J. L.) all presented an essentially identical clinical picture.

The common denominator in all our patients was the maximally increased pulmonary vascular resistance, i.e., pulmonary vascular obstruction. This was demonstrated physiologically in our five patients with adequate catheter studies and could be assumed from the demonstration of pulmonary vascular changes in the two autopsied cases. Thus pulmonary vascular obstruction syndrome presents a uniform clinical picture irrespective of whether or not it is associated with congenital heart disease.

In the *differential diagnosis* (Table III) of this syndrome the most important group for consideration is that of congenital heart disease with large left-to-right shunts with or without pulmonary arterial hypertension. Members of this group may be clinically identified by the well described characteristics of the individual lesions (i.e., auricular septal defect, ventricular septal defect and patent ductus arteriosus). This group as a whole can be distinguished from the pulmonary vascular obstruction syndrome by the x-ray finding of significant cardiac enlargement and the uniformly plethoric lung fields in the former. The physical examination reveals, in addition to the murmurs characteristic of the individual lesions, a hyperactive heart, deformity of the left chest and apical diastolic murmurs in a high percentage of cases. The past history of patients with large left-to-right shunts is replete with severe respiratory infections and episodes of congestive heart failure. Cyanosis and exertional dyspnea are not usually noted in the absence of congestive heart failure. Physiologically, this group differs from the pulmonary vascular obstruction group in that there is normal or only moderately increased pulmonary arteriolar resistance in the face of markedly increased pulmonary blood flow.

It is perfectly plausible, as has been repeatedly suggested, that patients with large left-to-right shunts may develop increased resistance in the pulmonary vascular bed through the years and thus ultimately present the picture of pulmonary vascular obstruction syndrome in later life.[8,9] This sequence of events may very well correspond to the development of the so-called

Eisenmenger's syndrome, with "cyanose tardive," from a large ventricular septal defect.[10] The syndrome of "reverse ductus" with disappearance of the characteristic murmur in older people may also correspond to this general pattern of evolution.[11,12] Our group of patients should be set apart from this group of patients with "secondary" increase in pulmonary arteriolar resistance on the basis of the presence of cyanosis from birth or early childhood, the absence of significant cardiomegaly and the generally stationary nature of their symptoms.

TABLE III

DIFFERENTIAL DIAGNOSIS OF THE PULMONARY VASCULAR OBSTRUCTION SYNDROME

		Pulmonary Vascular Obstruction	Large Left-to-right Shunt	"Eisenmenger's"	Pulmonic Stenosis
Sex		Predominantly female	No predilection	No predilection	
History	Cyanosis and clubbing	++ early	0	+ late	++
	Episodes of congestive failure	0	+	+	0
	Exercise intolerance	++ early	0	+ late	++
	Syncope	+	0	0	+
	Precordial pain	+	0	0	0
	Hemoptysis	+	0	+	0
	Increased number of upper respiratory infections	0	++	+	0
Physical Examination	Left chest deformity	0	++	++	0
	Loud P_2	++	+	++	0
	Loud systolic murmur	0	+	±	++
	Apical diastolic enlargement	0	+	+	0
X-ray	Right ventricular enlargement	++	+	++	++
	Left ventricular enlargement	0	?	±	0
	Prominent main pulmonary artery	+	++	++	++
	Pulmonary plethora	0	++	++	0
	Diminished peripheral vasculature	++	0	0	++
	Marked cardiomegaly	0	++	++	0

A third differential diagnostic problem is that of separating the pulmonary vascular obstruction group from patients with valvular pulmonic stenosis and patent foramen ovale or a ventricular septal defect. We know of two critically ill patients with a preoperative diagnosis of pulmonic stenosis in whom emergency thoracotomy revealed very high pulmonary arterial pressure. The symptomatology may be identical. Severe exertional dyspnea and mild cyanosis may be the chief complaints of both groups. The radiologic appearances are characterized by a prominent main pulmonary arterial segment, diminished peripheral pulmonary vasculature and right ventricular enlargement. The electrocardiograms show right ventricular hypertrophy. Even cardiac catheterization may fail to make the differential diagnosis if the pulmonary artery is not entered. The physical examination is the most reliable guide in the differential diagnosis of these patients—short of direct measurement of the pulmonary arterial pressure. The narrowly split second sound coupled with the harsh, well transmitted systolic murmur of pulmonic stenosis contrasts markedly with the loud, normal or narrowly split second sound and poorly transmitted blowing systolic murmur in pulmonary vascular obstruction. The phonocardiogram may be of some assistance in demonstrating these phenomena.

A wide variety of pathologic lesions in the pulmonary vascular bed have been described as the *anatomic substrates of pulmonary hypertension.*[13,14] These findings include, among others, atheromatous plaques, thrombi in various stages of organization, intimal and medial thickening of vessels of different calibers. In contrast to the group with definite vascular changes there is a minority of patients with pulmonary hypertension in whom careful

autopsy studies failed to reveal any significant pulmonary vascular disorder.[15] Dresdale[4] and others have therefore questioned the etiologic significance of the anatomic changes and suggest that these may be secondary to vasoconstriction of neurogenic origin.

The presence of cyanosis is sometimes equally difficult to explain anatomically in these patients. The *etiology of arterial unsaturation* is clearly understandable if the condition is associated with a septal defect, with patent foramen ovale or a patent ductus arteriosus. Two cases without defects at autopsy are cited by Ordway[16] who found arterial unsaturation even during inhalation of 100 per cent oxygen. He discarded the respiratory tract as an etiologic factor. In cases of this sort and perhaps in others as well, minute pulmonary arteriovenous shunts may be the factors explaining cyanosis. Lesions of this type have been demonstrated by Farber[17] in a patient with Eisenmenger's disease. If lesions of this nature are present in patients with pulmonary vascular obstruction syndrome, the assumption that pulmonary venous blood is fully saturated may not always be correct. As pointed out previously, this may considerably affect the validity of some of the calculations derived from data obtained at cardiac catheterization.

The etiology of increased pulmonary resistance is obscure in many instances. Excluding the well substantiated etiologic factors already mentioned (mitral stenosis, parenchymatous pulmonary disease, kyphoscoliosis, syphilis), two general groups have to be considered. In one, pulmonary vascular obstruction is associated with congenital heart disease, in the other it is not. The congenital cardiac anomaly is usually implicated through its long-term effect in increasing pulmonary blood flow[9] although, in fact, no definite correlation between the size of the septal defect and the degree of pulmonary vascular obstruction exists. Atrial septal defects are usually associated with the largest shunts[8] but are less likely to be accompanied by pulmonary arterial hypertension than ventricular septal defect and patent ductus arteriosus. Edwards[18,19] demonstrated persistence of the fetal type arterioles in the lungs of patients with large septal defects and with coarctation of the aorta and a "distal ductus." He regards this as a mechanism by which systemic blood pressure can be maintained at suitable levels in the face of a physiologically single ventricle, also as a protective mechanism against pulmonary edema. Although this mechanism may very well be the determining factor in a number of instances, it can hardly account for pulmonary vascular obstruction in cases with small defects.

Several factors, i.e., thromboembolic phenomena,[20] inflammation, neurogenic influences,[4] have been considered as etiologic agents in cases of pulmonary hypertension without congenital heart disease. No conclusive proof has been offered for any of these mechanisms.

The pulmonary vascular obstruction syndrome may be due to a number of etiologic factors, including congenital heart disease, notably ventricular septal defect,[8,9] which seems to be the most common associated lesion. We believe, however, that the presence of an associated congenital heart lesion does not exclude the co-existence of independent—possibly genetically associated—pulmonary vascular disease, and that the seven patients presented here are more closely related to the general category of "primary" pulmonary vascular disease than to the so-called Eisenmenger's group.

Essential pulmonary hypertension, according to data in the literature, is a relatively rapidly progressive syndrome. Wood[7] cites the average survival rate as two years beyond the onset of symptoms. None of our patients showed this rapid progression. J. C., our patient with the most rapidly downhill course, died about ten years after the onset of symptoms. The symptomatology of the remaining six patients has been stationary in some instances for as long as twenty to thirty years (J. Z., B. H.). The relatively benign course of some of these patients may be due to the co-existence of a congenital cardiac defect acting as an escape valve.[7]

In spite of this relatively long survival beyond the onset of symptoms, these patients are prone to sudden death, as exemplified in two of our cases (J. C. and S. H.). Patients with pulmonary vascular obstruction do not tolerate procedures of any sort well. One of our patients died during cardiac catheterization and another shortly following a decholin circulation time. We are also acquainted with the case history of a patient with this condition who died following an angiocardiogram.

There is some evidence from the literature and from our own material that syncope and precordial pain are usually very poor prognostic signs.[4]

Treatment. No treatment thus far advocated has been known to exert any significant influence on the course or prognosis of pulmonary vascular obstruction. Oxygen inhalation therapy in repeated daily administrations has been advised on the basis that pulmonary vascular spasm may be due to anoxia.[21,22] However, many of these patients are not severely anoxic and any relief afforded by this treatment is, by definition, only temporary. Antispasmodics, priscoline® in particular,[4] have been used and have been claimed to exert a beneficial effect. It is quite conceivable that pulmonary vascular spasm may be reduced but the occlusive organic changes could hardly be affected. There is, as yet, inadequate experience with this type of treatment. The authors believe that prolonged anticoagulant therapy aimed at the prevention of thrombotic phenomena may be an approach worth investigating in the treatment of these patients.

The demonstration of an operable congenital cardiac lesion (atrial septal defect or patent ductus arteriosus) introduces the problem of surgical management under these circumstances. Although the surgical repair of a defect permitting a sizeable left-to-right shunt would certainly be recommended, even in the face of pulmonary arterial hypertension, closure of such a defect cannot be expected to help if no significant left-to-right shunt exists. There is some evidence from our material and from data collected from the literature that if surgery under these circumstances is attempted the patient either does not survive or is not significantly benefited.

This line of thought has resulted in a concept according to which patients with operable congenital heart lesions and pulmonary arterial hypertension are divided into two groups in regard to surgery, i.e., those with marked elevation of pulmonary artery pressure due principally to large shunts are subjected to operation, whereas those with high pulmonary arterial resistances and no significant left-to-right shunts are treated medically.

SUMMARY

1. Seven patients with pulmonary vascular obstruction syndrome are discussed. The characteristic clinical and physiologic data are presented.

2. The relationship between increased pulmonary vascular resistance and congenital heart disease is discussed.

3. It is suggested that patients with maximally increased pulmonary vascular resistance should be classified as a separate group, irrespective of whether or not they have congenital heart disease.

4. The therapeutic implications are considered.

Acknowledgments: The authors would like to express their appreciation to Dr. Benjamin Castleman and Dr. Allen M. Butler for their permission to include Case VI in this report and for furnishing the illustrations pertaining to this case. We are also indebted to Dr. John M. Craig and Dr. Sidney Farber for the autopsy protocol and photomicrogram pertaining to Case VII.

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Effects of Diet in Essential Hypertension*

III. Alterations in Sodium Chloride, Protein and Fat Intake

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THE rice-fruit diet of Kempner has been found to be efficacious in essential hypertension but an unpalatable, monotonous regimen which could not be administered for prolonged periods of time to most patients.[1] This diet markedly restricts the intake of sodium chloride, protein, fat and cholesterol. At the present time there is no definite evidence indicating that restriction of any of these components except the sodium ion has value in the treatment of hypertensive vascular disease. It was the purpose of this study to obtain further information with regard to diversification of the regimen without sacrifice of its beneficial effects.

In a previous report[1] the effects of hospitalization alone in eighty-six patients and of the unmodified rice diet in fifty patients with severe essential hypertension were presented. Hospitalization on a control diet for a mean period of nine weeks resulted in decreases of more than 10 mm. Hg in basal diastolic blood pressure in 20 per cent of eighty-six cases. Improvement occurred in symptoms, electrocardiograms, transverse cardiac diameter and retinopathy in a moderate number of these patients.

Following the control period fifty patients whose blood pressure remained substantially elevated were studied for a mean period of ten weeks on the unmodified rice diet regimen. The results (Table 1) confirmed in all essentials the claims made by Kempner: (1) A decrease of at least 10 mm. Hg in the basal diastolic pressure occurred in 72 per cent of the series. The final basal blood pressure was less than 160/95 mm. Hg in 40 per cent of the series. (2) Symptomatic improvement (42 per cent) during rice diet therapy was greater than that observed in the controlled hospitalization study (18 per cent). (3) During the rice diet treatment two types of changes in the electrocardiogram occurred: flattened or inverted T waves became more upright or less deeply inverted; and depressed S-T segments tended to become isoelectric. (4) Favorable effects observed in the optic fundi included lessening of arteriolar spasm and pallor and decreases in hemorrhages, exudates and edema of the retina or the optic nerve-head. (5) Weight loss was not a serious problem. The average decrease in body weight was 2.5 kg., and the larger decreases nearly always were due to diuresis in patients with heart failure. Metabolic studies revealed that approximate nitrogen balance was achieved in most patients after a six-week equilibration period. The diet caused substantial decreases in blood urea nitrogen concentration, especially when elevated levels were present.

Despite these beneficial results, clinical trial of the rice diet in the hospital and in the outpatient department forced the authors to conclude that the unmodified regimen was impractical for use in general medical practice. The principal difficulties encountered were the necessity for exercising rigid control over the sodium intake

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and the unwillingess of most patients to adhere to the unmodified regimen for long periods of time.

In the previous report[1] preliminary data were presented on some modifications of the basic rice diet. Three of six patients showed rises in diastolic blood pressure following the addition of 1 to 3 gm. of NaCl to this regimen. The addition of salt-poor protein* and fat* to the diet seemed to have no deleterious effect in twenty-two patients.

TABLE I
SUMMARY OF PREVIOUS REPORT OF EFFECT OF HOSPITALIZATION AND THE KEMPNER RICE DIET IN PATIENTS WITH ESSENTIAL HYPERTENSION

	Prolonged Hospitalization on Control Diet		Effects of Kempner Rice Diet (Unmodified)	
	No. of Patients	Per cent	No. of Patients	Per cent
Diastolic blood pressure				
Total no. patients	50	..	50	..
Mean (before treatment)	115 mm. Hg		112 mm. Hg	
Mean (after treatment)	112 mm. Hg		96 mm. Hg	
Fall ≥10 mm. Hg	9	18	36	72
No change, ±10 mm. Hg	35	70	14	28
Rise ≥10 mm. Hg	6	12	0	0
Final pressure ≤95 mm. Hg	8	16	26	52
Electrocardiograms				
Total abnormal	29	..	27	..
Improved	2	7	9	33
No change	27	93	18	67
Worse	0	0	0	0
Transverse cardiac diameter				
Total no. patients	33	..	33	..
Decrease ≥1 cm.	2	6	19	58
No change, ±1 cm.	28	85	14	42
Increase ≥1 cm.	3	9	0	0
Retinopathy				
Total abnormal	36	..	36	..
Improved	9	25	27	75
No change	22	61	9	25
Worse	5	14	0	0
Weight change				
Total no. patients	50	..	50	..
Range	−9.1 to +5.7 kg.		−9.0 to +5.0 kg.	
Mean	+1.3 kg.		−2.5 kg.	

The findings of other investigators[2–14] on modifications of the rice diet or other low-sodium dietary regimens are summarized in Table II. Sodium chloride has been added to the restricted diets of sixty-two patients in amounts ranging from 1 to 20 gm. Thirty-eight of the sixty-two patients demonstrated unmistakable increases in blood pressure from the levels achieved with sodium restriction. Determination of the minimum amounts of sodium addition to the diet that would restore diastolic blood pressure to control levels was not reported.

Protein additions to basic diets have also been studied by others. Lonalac,® proteinum,® calcium caseinate or meat has been administered to fifteen patients. These additives were not shown to produce significant changes in blood pressure, retinopathy, electrocardiogram, transverse cardiac diameter or body weight. A few studies are available in patients receiving low-sodium (less than 1 gm. per day NaCl) diets which contained substantially more protein and fat than are present in the rice diet. The largest series was that of Bryant and Blecha[13] who reported forty-five patients treated in an outpatient clinic. Thirty-four of these patients showed a definite fall in diastolic blood pressure. Four other studies on hospitalized patients[2,8,12,14] demonstrated a fall in blood pressure in twenty-two of twenty-four patients. In contrast, a controlled blindfold study of seven patients by Landowne and his associates[10] failed to show an important hypotensive response.

The evidence accumulated thus far is consistent with the prevailing thought that sodium restriction is the important principle in the dietary treatment of hypertension. The amount of protein and fat in the diet did not appear to influence blood pressure levels to any significant degree if the low sodium content of the diet was maintained.

MATERIAL AND METHODS

Patients Studied. Only patients with primary or "essential" hypertension were included in this study. Initial blood pressure readings were 200/120 mm. Hg or higher, except in a few patients who presented other manifestations of the disease of special interest. In general the patients were considered to be severely ill from the viewpoint of blood pressure level, symptoms or complications of the disease.

Over the past four years 201 patients have been studied in the hypertension project. Investigations of one or more modifications of the rice diet or of the special low-sodium diet have been completed in forty-seven of these subjects. The disposition of the remaining 154 patients was as follows: thirty patients died before studies could be completed; twelve patients left the hospital against advice; thirty-four patients exhibited declines in blood pressure to near the normal range during the control period; twenty-two patients were unable to cooperate because

* Lonalac donated by the Mead Johnson Company, Evansville, Ind.

TABLE II

SUMMARY OF RECENT LITERATURE ON MODIFICATIONS OF LOW SODIUM DIETS*

Authors	Hosp. or OPD Study	No. of Patients	Basic Diet	Weeks on Basic Diet	NaCl Addition (gm.)	Protein Addition (gm./day)	Weeks on Modified Diet	Diastolic B.P. Δ ≥ 10 mm. Hg			EKG (N.C.)	Retina			Transverse Cardiac Diameter Δ > 1 cm.			Weight Δ > 1 kg.		
								Rise	N.C.	Fall		I	N.C.	W	I	N.C.	W	Rise	N.C.	Loss
Dole et al.[2]	Hosp.	4	<7 mEq. Na/day	10–26	10		2½	3	1	0	..	..	..	..	..	1	3	1	3	..
Corcoran et al.[5]	Hosp.	5	0.2 gm. Na or Rice	2–16	2.4– 7		2–12	2	3	0	5	1	4	..	..	5	..	..	..	..
		1	Rice	16	.....	Lonalac 30–60	12	0	1	0	1	1	..	..	..	1	..	..	..	..
		1	Rice + 0.4 gm. NaCl	5	.....	Proteinum 68	6	0	1	0	..	..	1	..	..	..	..	..	..	..
	OPD	3	0.2 gm. Na	12–32	6		6–14	1	2	0	..	..	..	..	..	..	..	..	..	..
Currens et al.[4]	Hosp.	6	Rice	3– 6	9		2	1	5	0	..	..	..	..	..	..	..	..	..	..
Chapman et al.[5]	Hosp.	5	Rice	6– 7	.....	Lonalac 40	2– 6	0	4	1	5	..	5	..	..	5	..	0	3	0
	Hosp.	3	Rice	6– 7	10		3	3	0	0	3	..	3	..	..	..	..	..	..	..
	OPD	2	0.4 gm. Na	.....	.....		7	1	1	0	..	..	..	..	..	..	..	..	..	..
Williamson[6]	Hosp.	3	Rice	4– 8	.....	Lonalac 40	3– 4	0	3	0	..	..	..	..	..	..	..	..	..	..
	Hosp.	4	Rice	4– 8	8–10		2	3	1	0	..	0	0	1	..	..	..	..	..	..
Dole et al.[7]	Hosp.	6	Rice	10–14	2.5		4	2	3	1	..	..	6	..	1	5	..	4	2	..
	Hosp.	1	Rice	10–14	10		....	1	0	0	..	..	1	..	..	..	1	1	..	..
Bang et al.[8]	Hosp.	7	0.3 gm. Na	.....	4.5		1– 5	4	3	0	..	..	..	..	..	..	..	..	..	..
Cameron et al.[9]	Hosp.	3	Rice	.....	.....	Ca caseinate 40	....	0	3	0	..	..	..	..	..	..	..	..	..	..
		11		3–13	1– 3		....	8	3	0	..	..	..	..	..	..	..	..	..	..
		1		4	7.5		1	1	0	0	..	..	..	..	..	..	..	..	..	..
Landowne et al.[10]	Hosp.	7	0.3 gm. Na	6	4		6	3	4	0	..	..	..	..	..	..	..	..	6	1
Kempner[11]	OPD	2	Rice	6+	.....	Meat 30†	8–12	..	2	0	..	..	..	..	..	..	..	..	..	..
Perera and Blood[12]	Hosp.	2	0.25–0.35 gm. Na	2, 7	4		1, 4	2	0	0	..	..	..	..	..	..	..	..	..	..
		6	4 gm. Na	3	11		1	3	3	0	..	..	..	..	..	..	..	6	..	..
Bryant and Blecha[13]	OPD	45	0.2 gm. Na	Variable	.....		....	6	5	34	..	..	..	..	..	..	..	..	..	..
Grollman et al.[14]	OPD	2	<1 gm. Na	4	20		1, 3	2	0	0	..	..	..	..	..	..	..	..	..	..

* Key to tables:
I.—Improved
W.—Worse
N.C.—No Change
Abn.—Abnormal
N.—Normal
C.—Control
R.—Rice
Low Na—Special Low Sodium Diet (94 mg. Na./day)
Prot.—Protein
Mod.—Diet Modification
Gr.—Grade[16]

† "Small amounts of non-leguminous vegetables, potatoes, lean meat or fish may be added."

of severe illness or social or psychologic problems; eight patients were given treatment other than the rice diet; eight patients were found to have chronic glomerulonephritis; forty patients completed satisfactory periods on the basic rice diet but were not studied further because of failure to respond to the rice diet or unwillingness to remain in the hospital for a longer time.

The forty-seven patients whose data form the basis of this report are therefore highly selected. They were included in the study only if the following criteria were met: (1) The blood pressure did not significantly decrease on hospitalization alone during an adequate control period. (2) There was a significant fall in blood pressure on the unmodified rice diet. A decrease of at least 10 mm. Hg in the mean basal diastolic blood pressure was arbitrarily selected as the criterion for a significant blood pressure response to the rice diet. It is believed that such a change is significant in terms of the method employed for measuring and recording blood pressure but no inference is made that this figure is of clinical importance. (3) The patients remained in the hospital for a sufficient time to study the effects of various alterations of the rice diet. Two of the forty-seven patients had edema of the optic discs and eight had blood urea nitrogen values greater than 20 mg. at the end of the control period.

There were twenty-six males and twenty-one females in the group to be reported. The males ranged in age from forty to sixty-six years (average fifty-three years) and the females from thirty-six to sixty-seven years (average fifty years).

Dietary Regimens. The composition of the control, rice and special low-sodium diets is outlined in Table III. The salt-poor diet maintained during the control period was served from the regular hospital diet kitchen. Analyses showed this diet to vary in NaCl content between 25 and 53 mEq. per day (approximately 0.6–1.2 gm. Na), a low range for a diet of this type.

a. Rice diet: The unmodified rice diet was prepared according to Kempner's specifications and served from a special kitchen. The diet provides 300 gm. (dry weight) of rice daily, sucrose and fresh or water-packed fruits and fruit juices.

TABLE III
COMPOSITION OF DIETS

	Control	Rice	Special Low-sodium
Calories per day	2220	2390	2140
Protein gm./day	85*	29*	90
Carbohydrate gm./day	280	560	320
Fat gm./day	85	3*	55
Cholesterol, gm./day	1.0*	0*	0.04*
Sodium gm./day	0.9 (40 mEq.)*	0.09 (4 mEq.)*	0.094 (4.1 mEq.)*
Potassium, gm./day	3.1 (80 mEq.)*	3.3 (85 mEq.)*	4.1 (106 mEq.)*
Chloride, gm./day	3.6 (100 mEq.)*	<0.36 (10 mEq.)*	>0.36 (10 mEq.)

* Determined by analysis; all other values estimated.

b. Supplements: The supplements to the rice diet included the following: sodium chloride in uncoated capsules or tablets, protein (with some fat) in the form of lonalac and protinal,®* vegetables and vegetable oils. Lonalac is a low-sodium milk powder which provides 7 gm. of protein, 7 gm. of fat and 10 gm. of carbohydrate per 200 cc. serving when diluted with water as indicated on the container. In some instances 20 gm. of protinal, a protein-carbohydrate powder, was added to each serving of lonalac. This enriched the protein content by 12 gm. and the carbohydrate content by 8 gm. per serving. The vegetables were selected from those low in sodium and are listed in the description of the special diet. The vegetable oils used were peanut oil and Wesson oil.® In addition to these foods, coffee,† matzohs‡ and pure fruit preserves were added to the rice diet in a number of instances for the sake of variety, after early trial indicated that they exerted no effect on blood pressure or other measurements.

c. Special low-sodium diet: The special low-sodium diet was designed to provide a selection of

* National Drug Co., Philadelphia, Pa.

† Borden's Instant Coffee donated by the Borden Co., New York, N. Y.

‡ Matzohs donated by A. Goodman & Sons, Long Island City, N. Y.

foods as nearly normal as possible while preserving the extremely low-sodium content of the rice diet. A liberal protein intake of 90 gm. per day was allowed; fat intake was moderately restricted to 55 gm. per day. An estimated 40 mg. per day of cholesterol was provided; this very low level was achieved by the omission of dairy products and the use of lonalac in which four-fifths of the fat content is derived from a vegetable source.

A sample menu of the special low-sodium diet for one day appears in Table IV. Three similar menus were used in rotation. When cooking was necessary, foods were steamed, broiled or fried in peanut or Wesson oils.

The lean fresh meats provided in the diet were beef, lamb and breast of chicken. Fresh fish, excluding shellfish, might also be permitted, although none was served during this study.

The following fresh vegetables which are low in sodium content were used: cabbage, asparagus, okra, beans (green or lima), egg plant, mushrooms, onion, squash, peas, corn, potato (white or sweet), lettuce, tomato, cucumber, green pepper and radishes. Macaroni, spaghetti and rice were used alternatively with potato. Fresh or water-packed fruits were used.

d. Other additions: During the periods on the basic or modified rice diets and the special low-sodium diet each patient received one vi-penta perle forte®* and 0.2 gm. ferrous sulfate daily to meet essential requirements. In addition a placebo capsule was given with each meal. Its content of 1 gm. of sucrose could be replaced by sodium chloride without the patient's knowledge.

e. Control of NaCl intake: The sodium content of the rice and special low-sodium diets was determined from time to time by flame photometry. It was found necessary to use water for cooking which had been passed through an ion exchange column. The urinary excretion of chloride was determined semi-quantitatively at least twice weekly in all patients who were on the several low-sodium regimens. Patients who gave persistent evidence of deviation from the prescribed regimen were separated from the study.

Length of Periods of Study. The control period was at least six weeks in length, except in a few severely ill patients who exhibited rapidly increasing blood pressure. With these exceptions the period was adequate for the establishment of a fairly stable basal blood pressure. The period on the unmodified rice diet was at least six weeks in length and usually was of eight or more weeks' duration. The special low-sodium diet and modifications of the rice diet were maintained for at least four weeks before further dietary changes were made. In some of the experiments with NaCl addition the period of study was only three weeks. Throughout the studies changes in the diet were not made until at least two successive weekly mean blood pressures showed little variation.

TABLE IV

SPECIAL LOW-SODIUM DIET, SAMPLE MENU

Breakfast	Fresh orange and grapefruit sections —100 gm.
	Rolled oats—20 gm., dry weight
	Matzoh—20 gm.
	Fresh fruit preserves—25 gm.
	Lonalac—200 cc.
	Protinal—20 gm.
	Coffee—2 gm., dry weight
	Sugar—20 gm.
Lunch	*Broiled lean steak—50 gm.
	*Mushrooms—50 gm.
	*Onion—50 gm.
	*Sweet potato—100 gm.
	Lettuce—25 gm.
	Fresh sliced tomato—50 gm.
	(+ lemon slice)
	Matzoh— 20 gm.
	Fresh fruit preserves—25 gm.
	Lonalac—200 cc.
	Protinal—20 gm.
	Fresh blueberries—100 gm.
2:00 P.M.	Fresh sliced pear—100 gm.
	Grape juice—200 cc.
Dinner	*Breast of chicken—50 gm.
	*Fresh peas—50 gm.
	Rice—30 gm., dry weight
	Lettuce—25 gm.
	Fresh sliced cucumber—50 gm.
	Fresh sliced pepper—25 gm.
	Matzoh—20 gm.
	Fresh fruit preserves—25 gm.
	Lonalac—200 cc.
	Protinal—20 gm.
	Fresh sliced pineapple—100 gm.
8:00 P.M.	Orange and grapefruit juice— 200 cc.

* Raw weight.

Hospital Study of Patients. An extensive investigation was performed in each patient during the control period. In the early phase of this investigation these studies were repeated *in extenso* during each dietary period. However, when the measurements which showed changes due to dietary treatment had been determined, the repeat studies were limited to these features:

* Vi-Penta Perles Forte donated by Hoffmann-La Roche, Inc., Nutley, N. J.

blood pressure, inspection of the optic fundi by ophthalmologic consultants, electrocardiogram, transverse cardiac diameter (6-foot x-ray film), body weight and blood urea nitrogen. Emphasis will be placed on these six items throughout the report. Detailed studies of the serum lipid patterns were performed and will be reported elsewhere.[15]

Method of Taking and Recording Blood Pressure. Blood pressures were taken by physicians and nurses with a mercury sphygmomanometer three mornings weekly in each patient. The measurements were made while the patient was lying in bed and before anything more than minimal activity had been undertaken. Three readings were made each time and the lowest systolic and diastolic pressures observed were designated as the basal blood pressures for that day. The three basal pressures obtained in each week were averaged and the mean blood pressure for the week was used for statistical analysis.

The blood pressures recorded in this presentation are designated as final pressures on the control, rice or other diets. The final control and rice diet blood pressures are the averages of the last three weekly pressures of the periods on those diets. For the periods of modified rice or special low-sodium diets the final blood pressures are the averages of the last two or three weekly pressures, depending on the length of the period. These recorded pressures are thus the average basal blood pressures observed on six or nine occasions after sufficient time had elapsed for appearance of the effects of the dietary changes. In the presentation of the results of these investigations emphasis will be placed almost entirely upon the changes observed in diastolic blood pressure.

RESULTS

The observations following the addition of sodium chloride, protein, vegetables and vegetable oils to the rice diet will be presented separately. Finally the results of trial on the special low-sodium diet will be discussed. All patients who completed programs of study are reported here; in some instances this includes studies mentioned in the previous papers of this series.[1] Under each section changes in blood pressure, retinopathy, transverse cardiac diameter, electrocardiogram, body weight and blood urea nitrogen will be presented in tabular form when sufficient data are available. Significant changes were considered to have been effected when the following criteria were satisfied: (1) blood pressure—a change in diastolic pressure of 10 mm. Hg or more; (2) eyegrounds—definite change in arteriolar spasm or pallor, retinal edema, hemorrhages or exudates, and papilledema; (3) transverse cardiac diameter—change of 1 cm. or more; (4) electrocardiograms—definite change in S-T segments and/or T waves; (5) weight—change of 1 kg. or more; (6) B.U.N.—change of 10 mg. per 100 cc. or more.

Supplementation of Basic Low-Sodium Diets with Sodium Chloride. 1. Addition of 3 gm. sodium chloride at the beginning of rice diet treatment: In order to evaluate the psychologic effects of treatment with the rice diet 3 gm. per day of sodium chloride were substituted for the sucrose placebo capsules during the first three to six weeks. This study was performed in thirteen patients. (Table v.) There were no significant blood pressure changes *during* the period of salt supplementation except for a decrease of 21 mm. in the systolic pressure of one patient. *Following* withdrawal of the sodium chloride in the capsules the patients were maintained on the unmodified rice diet for at least six more weeks. At the end of the latter period the diastolic blood pressures showed significant decreases in four patients with a maximum decrease of 17 mm. Hg. Seven patients showed little change and two showed significant increases in diastolic pressure on the rice diet. The average difference between the final control and final rice diet blood pressures for the entire group was −13/−3 mm. Hg (systolic/diastolic).

Data on eyeground changes are available in eleven of these patients. Retinal findings at the end of the control period were compared with observations after a preliminary period on the rice diet plus NaCl and a subsequent trial on the unmodified rice diet. Improvement was noted in four patients while four others showed worsening of their retinal lesions.

In the ten patients whose electrocardiograms were compared at the end of the rice diet period with tracings in the control period, changes in the direction of normality occurred in five patients. Exaggeration of the abnormal features occurred in three subjects.

Four of the twelve patients with adequate data showed decreases of more than 1.0 cm. in transverse cardiac diameter and the remainder showed no significant change. The average reduction observed in the series was 0.9 cm.

TABLE V

3 GM. NACL ADDED DURING EARLY WEEKS ON RICE DIET*

Patient	Sex and Age	Weeks on Rice + NaCl	Final Control B.P.	Final Rice + NaCl B.P.	Δ B.P.	Δ Weight (kg.) on Rice + NaCl	Subsequent Trial on Rice Diet						Δ Weight (kg.) R + NaCl vs. R	Blood Urea N (mg. %)		
							Final Rice B.P.	Final B.P. Δ from Control	Eyegrounds		EKG		Cardiac Diameter Δ (cm.)			
									Grade	Δ	Control	Δ				
														C	R + NaCl	R
A. Wa.	F, 47	4	158/ 84	160/ 85	+ 2/+1	+0.7	163/ 83	+ 5/− 1	2	W	Abn.	I	−0.3	−0.5	..	..	..
C. V.	F, 52	6	167/100	171/100	+ 4/ 0	.....	156/ 93	−11/− 7	2	N.C.	Abn.	I	+0.1	.....	..	..	..
A. D.	M, 44	3	170/107	173/108	+ 3/+1	−0.9	137/ 90	−33/−17	1	W	N	N.C.	−2.1	−2.0	..	..	..
A. A.	M, 65	4	196/109	195/108	− 1/−1	−1.5	178/ 97	−18/−12	..	....	Abn.	W	0	−1.9	..	..	..
F. R.	M, 40	4	172/121	173/121	+ 1/ 0	−1.1	175/123	+ 3/+ 2	2	W	Abn.	W	−0.4	+1.7	12	15	5
A. H.	M, 54	4	223/128	227/130	+ 4/+2	+0.1	220/126	− 3/− 2	2	N.C.	Abn.	I	−0.1	−0.2	30	11	..
A. Wi.	M, 65	4	221/ 99	230/103	+ 9/+4	+0.6	183/ 84	−38/−15	2	I	Abn.	N.C.	−0.6	−1.4	..	..	..
C. K.	F, 54	6	211/105	190/103	−21/−2	−1.3	182/107	−29/+ 2	3	I	Abn.	I	−0.3	.....	21	8	9
A. M.	F, 44	4	203/115	204/114	+ 1/−1	+0.1	205/121	+ 2/+ 6	2	W	Abn.	I	−0.6	−0.5	17	5	9
C. A.	M, 58	4	219/101	217/106	− 2/+5	−1.7	182/ 90	−37/−11	3	I	....	....	−3.2	−8.1	9	7	9
M. S.	F, 67	5	180/ 91	172/ 87	− 8/−4	+0.6	168/ 84	−12/− 7	2	I	....	....	.....	+0.4	..	..	..
J. W.	M, 61	6	203/ 90	206/ 85	+ 3/−5	−1.2	187/104	−16/+14	..	....	Digitalis		−1.4	−2.5	..	..	..
J. K.	M, 49	5	199/110	192/106	− 7/−4	−1.4	219/125	+20/+15	3	N.C.	Abn.	W	−1.6	−3.4	..	..	..
Average			194/105	193/104	− 1/−1	−0.6	181/102	−13/− 3	..	....	....	....	−0.9	−1.7	..	..	..

*Key to tables:

I.—Improved
W.—Worse
N.C.—No Change
Abn.—Abnormal
N.—Normal
C.—Control
R.—Rice
Low Na—Special Low Sodium Diet (94 mg. Na./day)
Prot.—Protein
Mod.—Diet Modification
Gr.—Grade

In this group of thirteen patients there was an average loss of 0.6 kg. of body weight during the initial period of salt supplementation. Elevated blood urea nitrogen levels were lowered in three of five patients during the NaCl supplementation.

decreases of at least 10 mm. Hg in diastolic blood pressure. This supplementation was followed by an average change in blood pressure of +4/+3 mm. Hg. A significant change in diastolic blood pressure occurred in only one subject. (Table VI.) Six patients gained an aver-

TABLE VI

ADDITION OF 0.5 GM. NACL AFTER TRIAL ON RICE DIET OR SPECIAL LOW-SODIUM DIET*

Patient	Sex and Age	Diet	Weeks on Modification	Final Control B.P.	Final B.P. Before NaCl Added	Final B.P. After NaCl Added	Δ B.P. with NaCl 0.5 gm.	Δ Weight (kg.) with NaCl 0.5 gm.	Blood Urea N (mg. %)		
									C	Rice or Low Na	+ NaCl
A. Wi.	M, 65	R	3	221/ 99	183/ 84	174/ 84	− 9/ 0	+0.1	..	..	..
A. B.	F, 35	R	4	208/130	163/104	166/107	+ 3/+ 3	.....	..	..	..
H. C.	M, 63	R	8	165/110	146/ 94	144/ 97	− 2/+ 3	+2.3	..	..	..
F. S.	M, 66	R	3	200/101	155/ 89	145/ 85	−10/− 4	+0.5	25	6	7
S. R.	F, 36	Low Na	4	238/141	181/102	192/110	+11/+ 8	−0.5	..	..	..
M. W.	F, 55	Low Na	4	229/122	167/ 95	182/ 95	+15/ 0	+0.5	..	..	..
G. D.	M, 50	Low Na	4	184/115	139/ 76	158/ 87	+19/+11	+2.3	25	28	27
	Average		..	206/117	162/ 92	166/ 95	+ 4/+ 3	+0.9	..	..	..

* Refer to Table V for key.

The lack of a significant decrease in blood pressure in patients placed initially on the rice diet with 3 gm. of NaCl added shows that the diet possesses no anti-hypertensive properties in the presence of this amount of NaCl. The relatively poor blood pressure response in this group of patients after withdrawal of the added NaCl from the rice diet is an enigma. Statistical analysis demonstrated that the decreases of both systolic and diastolic pressures in these patients (average −13/−3 mm. Hg) were smaller than could be expected in a random sample of the series treated from the start with the unmodified rice diet (mean change −29/−16 mm. Hg). In addition the patients whose rice diet treatment was introduced with NaCl supplementation showed less favorable changes in eyegrounds, electrocardiograms and transverse cardiac diameter than occurred in the original series. Thus in some way not understood the addition of 3 gm. of NaCl during the first few weeks on the rice diet diminished the ultimate favorable effects as observed over the next eight weeks.

2. Addition of 0.5 gm. of NaCl after trial on rice or special low-sodium diets: One-half gm. of NaCl in tablet form was added to the diet of seven patients who had previously responded with

age of 0.9 kg. during the period of supplementation with 0.5 gm. NaCl. Other clinical data are not available in sufficient quantity.

3. Addition of 1 or 3 gm. of NaCl after trial on rice diet: One gm. per day of NaCl was substituted for sucrose in a placebo capsule for one female patient who had previously responded favorably to the rice diet. (Table VII.)

Three gm. NaCl supplements were given in a similar manner to four patients who had previously responded to rice diet treatment. (Table VII.) Two of the subjects exhibited a rise of more than 10 mm. Hg in diastolic pressure and the other two did not show a significant change in either direction. Electrocardiograms were taken in three of the patients: one improved, one became more abnormal and one did not change.

4. Stepwise addition of NaCl to the rice and special low-sodium diets: In five patients observations were made during the addition of successive small increments of NaCl to the rice or special low-sodium diets. Each level of NaCl intake was maintained for a period of three to eight weeks. The data are presented in Table VIII. When 0.5 gm. NaCl was added, the diastolic pressure increased by 10 mm. Hg in only one

subject. When the amount of NaCl was increased to 1 gm., two additional patients showed basal diastolic pressures at least 10 mm. Hg higher than the level attained with maximal sodium restriction. The remaining two patients showed rises in diastolic blood pressure exceeding 10 mm. Hg after reaching total NaCl supplements of 2 and 2.5 gm.

Observations are available in three of the patients indicating that the retinal findings were not changed following the addition of salt increments in the manner described. In two patients the electrocardiographic abnormalities increased during the addition of NaCl increments. Irregular weight changes averaging a gain of 1 kg. occurred with the first 0.5 gm.

TABLE VII

ADDITION OF 1 OR 3 GM. NACL AFTER TRIAL ON RICE DIET*

Patient	Sex and Age	Gm. NaCl Added	Weeks on Modification	Final Control B.P.	Final Rice B.P.	Final B.P. after NaCl Added	Δ B.P. with NaCl	Δ EKG with NaCl	Δ Cardiac Diameter with NaCl (Cm.)	Δ Weight kg. with NaCl
D. K.	F, 48	1	5	165/109	135/ 89	167/103	+32/+14	I	−0.1	+1.7
J. C.	F, 50	3	4	200/ 98	145/ 72	186/ 95	+41/+23	I	.....	.....
F. S.	M, 66	3	6	200/101	135/ 71	166/ 85	+31/+14	N.C.	−1.0	+0.8
P. K.	M, 61	3	6	150/ 97	117/ 84	119/ 81	+ 2/− 3	W	.....	−1.7
M. B.	F, 57	3	4	153/ 99	111/ 81	133/ 89	+22/+ 8	....	.....	+0.1
	Average		..	173/101	128/ 79	154/ 90	+26/+11	....	.....	.....

* Refer to Table v for key.

TABLE VIII

STEPWISE ADDITION OF NACL TO THE RICE DIET AND SPECIAL LOW-SODIUM DIETS*

Patient	Sex and Age	Diet	Gm. NaCl Added	Weeks in Period	Final B.P. of Period	Change in B.P. from Baseline on Low Na Regimen	Fundi	EKG	Δ Weight (kg.)	Blood Urea N (mg. %)
F. S.	M, 66	Control	...	..	200/101	.....	Gr. 2	....	.....	25
		Rice	0	9	155/ 89	.....	Imp.	....	.....	6
		Rice	0.5	3	145/ 85	−10/− 4	....	....	+0.5	7
		Rice	1.0	4	161/ 95	+ 6/+ 6	....	....	+1.2	..
		Rice	1.5	3	167/ 96	+12/+ 7	N.C.	....	+0.5	..
		Rice	2.0	3	178/ 98	+23/+ 9	....	....	−0.3	..
		Rice	2.5	3	189/100	+34/+11	....	....	+0.2	..
H. C.	M, 63	Control	...	..	165/110	.....	....	....	.....	..
		Rice	0	13	146/ 94	.....	....	....	.....	..
		Rice	0.5	8	144/ 97	− 2/+ 3	....	....	+2.3	..
		Rice	1.0	5	172/112	+26/+18	....	....	+0.2	..
M. W.	F, 55	Control	...	..	229/122	.....	Gr. 2	Abn.	.....	12
		Sp. Low Na	0	7	167/ 95	.....	....	W	.....	18
		Sp. Low Na	0.5	4	182/ 95	+15/ 0	....	....	+0.5	..
		Sp. Low Na	1.0	4	202/103	+35/+ 8	....	....	+0.2	13
		Sp. Low Na	2.0	6	231/118	+64/+23	N.C.	W	−1.6	9
G. D.	M, 50	Control	...	..	184/115	.....	Gr. 3	Abn.	.....	25
		Sp. Low Na	0	4	139/ 76	.....	....	I	.....	28
		Sp. Low Na	0.5	6	158/ 87	+19/+11	....	I	+2.3	27
		Sp. Low Na	1.0	6	161/ 92	+22/+16	N.C.	W	−0.5	27
S. R.	F, 36	Control	...	..	238/141	.....	....	....	.....	11
		Sp. Low Na	0	6	181/102	.....	....	....	.....	12
		Sp. Low Na	0.5	3	192/110	+11/+ 8	....	....	−0.5	..
		Sp. Low Na	1.0	4	194/112	+13/+10	....	....	+1.3	15

* Refer to Table v for key.

NaCl increment. Subsequent changes during periods on larger NaCl supplements were variable. Limited data in four patients of this group suggest that small supplements of NaCl do not influence the blood urea nitrogen level observed on either the rice or low-sodium diets.

extra protein. The effects observed were not correlated with the amount of protein added so that all of the patients may be reported together. (Table IX.) The course of one of these patients is charted in Figure 1.

Only two patients showed significant changes

TABLE IX

ADDITION OF LOW-SODIUM PROTEIN SUPPLEMENTS TO THE RICE DIET*

Patient	Sex and Age	Gm. Protein Added	Weeks on Modification	Final Control B.P.	Final Rice B.P.	Δ B.P. on Rice	Final B.P. after Protein	Δ B.P. after Protein	Eyegrounds		EKG Δ on Prot.	Weight (kg.) Δ on Prot.	Blood Urea N (mg. %)			Cardiac Diameter (cm.) Δ on Prot.
									Grade	Δ on Prot.			C	R	+ Prot.	
A. A.	M, 65	12	6	196/109	178/ 97	−18/−12	185/100	+ 7/+ 3	..	....	N.C.	−0.2	..	..	..	−0.5
S. D.	M, 52	12	8	215/133	204/122	−11/−11	185/115	−19/− 7	..	....	I	+1.3	..	..	..	+0.8
T. M.	M, 46	12	4	200/140	196/122	− 4/−18	213/136	+17/+14	3	I	N.C.	−0.5	25	5	8	.....
F. S.	M, 66	12	7	200/101	140/ 76	−60/−25	136/ 76	− 4/ 0	2	W	N.C.	+3.8	..	..	..	+0.9
M. K.	F, 54	12	5	237/125	208/109	−29/−16	233/118	+25/+ 9	3	N.C.	N.C.	+0.2	..	..	..	−0.5
J. N.	F, 46	30	5	216/132	194/106	−22/−26	207/111	+13/+ 5	4	I	W	+1.8	12	7	18	+0.4
C. R.	M, 49	30	7	201/109	185/ 98	−16/−11	182/102	− 3/+ 4	..	....	....	+1.3	..	..	..	+0.1
M. F.	M, 42	50	5	224/134	178/117	−46/−17	156/103	−22/−14	2	N.C.	I	+1.4	14	9	22	.....
S. R.	F, 36	50	6	238/141	205/115	−33/−26	202/118	− 3/+ 3	4	I	N.C.	+0.2	11	5	8	−0.8
	Average		..	214/125	187/107	−27/−18	188/108	+ 1/+ 1	..	....	....	+1.0	..	..	..	0.0

*Refer to Table v for key.

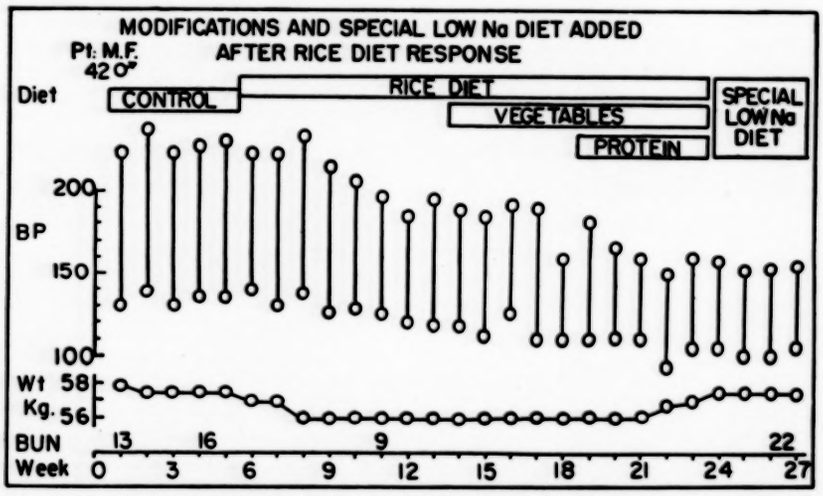

FIG. 1. Example of a patient who received rice diet after blood pressure had reached a steady state on a control diet containing 30 mEq. of sodium. After a response in blood pressure, vegetables and protein (50 gm./day as lonalac and protinal mixture) were added stepwise. When this regimen was discontinued and a 4 mEq. sodium–90 gm. protein diet substituted, the lowered blood pressure level persisted.

Addition of Low-Sodium Protein Supplements to the Rice Diet. Protein (and fat) in the forms of lonalac and protinal were added to the rice diet in nine patients who had met the criterion of a favorable blood pressure response to the unmodified rice diet. Five of the subjects received amounts providing 12 gm. daily of supplementary protein; two subjects received 30 gm. and the remaining two received 50 gm. of

in diastolic pressure; one an increase of 14 mm. Hg, the other a decrease of 14 mm. Hg. The mean change for all patients was +1/+1 mm. Hg. Data on eyegrounds are available in six patients of whom three showed improvement and one became worse. Electrocardiograms were taken in eight patients during the period of protein supplementation. The findings indicated improvement in two patients while one patient's

tracings became more abnormal. There was no significant change in transverse cardiac diameter. A mean weight gain of 1 kg. occurred during protein supplementation. In four subjects with adequate data the level of blood urea nitrogen during protein addition was slightly higher than that observed on the rice diet.

TABLE X

OBSERVATIONS WITH SPECIAL LOW-SODIUM DIET*

Patient	Sex and Age	Weeks on Rice	Weeks on Low Na	Final Control B.P.	Final Rice B.P.	Δ B.P. on Rice	Final B.P. on Low Na	Δ B.P. on Low Na	Eyegrounds		Δ EKG	Δ Weight (kg.)	Cardiac Diameter Δ cm.	Blood Urea N (mg. %)		
									Grade	Δ				C	R	Low Na
a. Patients with significant response to rice diet																
E. N.	M, 42	13	4	196/121	165/111	−31/−10	167/109	+ 2/− 2	2	N.C.	I	+1.7	.....	..	..	..
M. S.	M, 51	10	5	162/117	158/104	− 4/−13	177/104	+19/ 0	2	N.C.	....	+0.5	−0.7	25	10	26
G. D.	M, 50	10	4	184/115	147/ 89	−37/−26	141/ 78	− 6/−11	3	N.C.	....	+0.8	.....	25	8	28
J. M.	M, 44	14	12	209/113	143/ 95	−66/−18	158/ 94	+15/− 1	2	N.C.	....	−0.5	.....	22	9	24
B. F.	F, 52	6	4	228/105	188/ 85	−40/−20	185/ 84	− 3/− 1	..	....	....	−0.7	.....	..	..	..
J. R.	M, 48	7	12	183/113	157/ 97	−26/−16	174/105	+17/+ 8	2	N.C.	....	+1.5	.....	12	..	15
	Average		..	193/114	159/ 97	−34/−17	167/ 96	+ 8/− 1	..	....	....	.....	.....	..	..	..
b. Patients without significant response to rice diet																
J. K.	M, 49	6	8	198/110	220/120	+22/+10	200/ 96	−20/−24	3	N.C.	I	−4.2	+1.5	18	..	25
L. S.	M, 56	7	8	242/112	221/104	−21/− 8	209/100	−12/− 4	..	....	N.C.	+1.4	−0.4	..	..	..
D. W.	F, 52	8	5	163/108	139/104	−24/− 4	130/100	− 9/− 4	..	....	N.C.	.....	.....	25	6	17
	Average		..	201/110	193/109	− 8/− 1	179/ 99	−14/−10	..	....	....	.....	.....	..	..	..
c. Special low-sodium diet without preceding trial on rice diet																
R. C.	M, 48	..	7	209/135	202/113	+ 3/− 3	199/116	−10/−19	..	....	....	−1.9	−1.2	18	..	20
E. L.	F, 62	..	5	219/116	.....	.....	197/ 97	−22/−19	..	....	....	.....	.....	..	..	..
B. V.	F, 54	..	7	226/124	.....	.....	204/114	−22/−10	..	....	N.C.	+0.2	.....	30	..	53
	Average		..	218/125	.....	.....	200/109	−18/−16	..	....	....	.....	.....	..	..	..

* Refer to Table v for key.

Addition of Vegetables to the Rice Diet. Six patients who had responded to the basic rice diet received 200 gm. of low-sodium vegetables daily for periods of four to six weeks. In one patient the diastolic blood pressure increased by 10 mm. Hg. The other patients showed either no change or a further decline in blood pressure (mean −5/−5 mm. Hg).

Of four patients whose eyegrounds were examined two showed further improvement and two, no change. Likewise, of four patients with electrocardiograms available, two improved and two did not change. Only one of four patients showed a significant change in heart size, this a reduction of 1.1 cm. Weight changes during vegetable supplementation were variable.

Addition of Vegetable Oil to the Rice Diet. Twenty or 40 gm. per day of peanut or Wesson oils were added for a one-month period in five patients. There was no significant change in blood pressure in any case (mean −1/+2 mm. Hg). Funduscopic data in two subjects indicated further retinal improvement in one and no change in the other. In the three patients with adequate background data significant changes in transverse cardiac diameter did not develop. Changes in body weight were insignificant, except for a gain of 1.8 kg. in one of the five subjects.

Observations on Special Low-Sodium Diet. The special low-sodium diet may be considered to be a combination of many of the individual modifications of the basic rice diet which have been discussed in the preceding sections. The following types of studies have been conducted in patients on this diet: (*a*) Six patients who had shown a response to the rice diet were transferred to the special low-sodium diet to determine whether the beneficial effects achieved on the rice diet would be maintained or reversed. (*b*) Three patients who had not responded to the basic rice diet were transferred to the special diet to learn whether any fall in blood pressure could be achieved after failure on the rice diet. (*c*) Three additional patients were placed on the

special low-sodium diet after the control period and without preliminary "priming" with the rice diet. One of these subjects was subsequently transferred to the rice diet. (*d*) The course of four outpatients on the special low-sodium diet has been followed. Studies *a* and *b* will be discussed together, followed by separate mention of the findings in studies *c* and *d*.

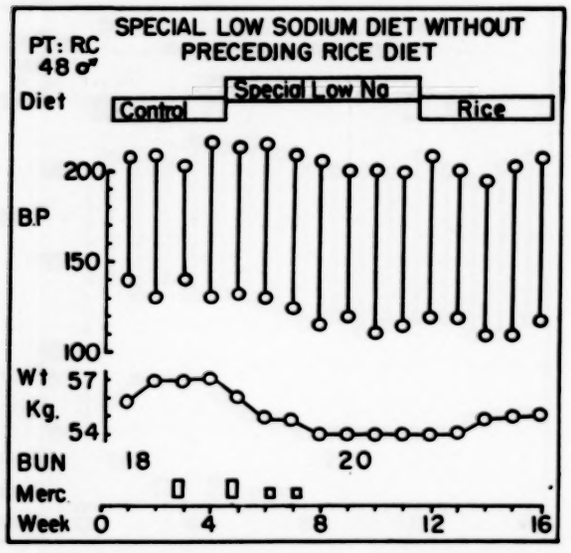

FIG. 2. Example of a patient who received the special low-sodium diet (4 mEq. sodium–90 gm. protein) after an appropriate period on a 30 mEq. Na diet. Diastolic blood pressure response persisted after the substitution of the rice diet. In this instance, because of cardiac failure, mercuhydrin was used to facilitate sodium depletion.

a, b. Rice diet followed by low-sodium diet: Of the six patients who responded to the rice diet none showed a significant change in diastolic blood pressure when transferred to the special low-sodium diet (average +7/−1 mm. Hg). (Table x *a*.) Of the five patients studied none showed a further change in the retinal picture. The data on electrocardiograms, transverse cardiac diameter and body weight are too limited to be summarized. Data available in six patients indicate clearly that the blood urea nitrogen on the low-sodium diet rose from the levels noted on the rice diet to the original control values.

One of the three subjects who failed to show a drop in blood pressure after six weeks on the unmodified rice diet did respond to subsequent treatment with the special diet by a decrease of 24 mm. Hg in diastolic pressure. (Table x *b*.) The other two patients in this group did not respond to either diet.

c. Low-sodium diet not preceded by rice diet: Three subjects were placed on the special low-sodium diet immediately following the control period. All showed a significant fall in diastolic blood pressure (average −18/−16 mm. Hg). (Table x *c*.) There was no further change in one of these patients when he was subsequently transferred to the unmodified rice diet. (Fig. 2.) No information is available on changes in retinopathy. In one patient whose electrocardiograms were uncomplicated by digitalis therapy no change from control tracings occurred. Only one subject had the requisite x-rays of the heart; there was a decrease in transverse diameter of 1.2 cm. There was a loss of 1.9 kg. of body weight in one patient and no change in another. The blood urea nitrogen level was higher than the control level in one subject and unchanged in another.

d. Low-sodium diet in outpatients: Observations upon the use of the special low-sodium diet at home have been made in four patients over periods of several months. Clinical evaluations have been made during three-day readmissions to the hospital. Three of the patients showed return of the original hypertensive blood pressure levels, with no change in the retinal findings from those observed at the end of the period of investigation in the hospital. One patient, who was the best situated to cooperate with the program at home, continued to have a significantly lowered blood pressure seven months after discharge. During this time his eyegrounds improved from grade IV to grade II. The malignant course of his disease appeared to have been arrested temporarily.

DISCUSSION

The results of the present investigation strongly support the generally accepted view that restriction of the intake of sodium is the effective principle of the Kempner rice-fruit diet. This is derived from the observations that (1) the rice diet has no effect on the blood pressure of hypertensive patients when supplemented from the outset with NaCl; and (2) addition of NaCl to the basic diet is usually soon followed by a return of blood pressure to original levels.

Our previous evaluation of the Kempner rice diet in the treatment of hypertensive cardiovascular disease demonstrated that a substantial decrease in the level of the blood pressure and improvement in other cardinal manifestations of the disease occurred in a moderate number of severely ill patients. However, the rigors of the

treatment were so great that most of our patients would accept the regimen for only limited periods of time. It was clear that if a more liberal regimen could be found which retained the efficacy of the rice diet, this serious obstacle might be overcome. A controlled experimental approach has been applied in the studies reported here to determine the extent of diversification of the rice diet which is permissible. The results obtained on the various dietary regimens are summarized in Table XI.

TABLE XI

SUMMARY OF RESULTS OF VARIOUS DIETARY REGIMENS*

Regimen	Δ ≥ 10 mm. Hg in Diastolic Blood Pressure					EKG				Retinopathy				Transverse Cardiac Diameter Δ ≥ 1 cm.				Body Weight Δ ≥ 1 kg.			
	No. of Patients	Av. Δ	Incr.	N.C.	Decr.	No. of Patients	I	N.C.	W	No. of Patients	I	N.C.	W	No. of Patients	I	N.C.	W	No. of Patients	Gain	N.C.	Loss
Part I. Comparison of: (1) Rice Diet; (2) Rice Diet Preceded by Rice + NaCl; (3) Special Low Na Diet																					
Rice diet	50	−29 / −16	0	14	36	27	9	18	0	36	27	9	0	33	19	14	0	50	5	23	22
Rice after rice plus 3 gm. NaCl	13	−13 / −3	2	7	4	10	5	2	3	11	4	3	4	12	4	8	0	11	1	6	4
Special low Na diet after control	3	−18 / −16	0	0	3	1	0	1	0	..	..	..	..	1	1	0	0	2	0	1	1
Part II. Effects of Supplements to Rice Diet																					
Rice plus 0.5 Gm. NaCl	7	+4 / +3	1	6	0	..	..	..	..	..	..	..	..	..	..	..	..	6	2	4	0
Rice plus 1–3 gm. NaCl	5	+26 / +11	3	2	0	4	2	1	1	..	..	..	..	2	1	1	0	4	1	3	0
Protein supplement	9	+1 / +1	1	7	1	8	2	5	1	6	3	2	1	7	0	7	0	9	5	4	0
Vegetable supplement	6	−5 / −4	1	4	1	4	2	2	0	4	2	2	0	4	1	3	0	6	1	3	2
Oil supplement	5	−1 / +2	0	5	0	1	0	1	0	2	1	1	0	3	0	3	0	5	1	4	0
Low Na diet after rice	6	+8 / −1	0	6	0	1	1	0	0	5	0	5	0	1	0	1	0	6	2	4	0

* Refer to Table V for key. The results of all of the dietary experiments are summarized above. In part I of this table are compared the effects of the rice diet when given without and with an introductory period of supplementation with NaCl. The observations in the three patients receiving the special low-sodium diet without a preceding period on the rice diet are included for reference. Part II of the table summarizes for ready reference the effects of the several supplements which were added to the rice diet.

The studies of addition of NaCl to the diet in small increments gave results which suggest strongly that most patients can assimilate without harmful effect more NaCl than is present in many very low-sodium diets, at least *after* a reduction of blood pressure has been achieved by rigid salt deprivation. The addition of protein, fat or low-sodium vegetables to the rice diet, or even a change to a markedly diversified diet of normal protein content, did not reverse the beneficial effects of preceding rice diet treatment. Indeed, very limited data indicated that the special low-sodium diet might be effective in the treatment of hypertension without "priming" with the basic rice regimen.

The special low-sodium diet clearly provides better nutriment and a more attractive variety of foods for the patient than does the rice diet. In our experience the diet was accepted well for prolonged periods, although rebellion ultimately occurred in a few patients. Weight control was easier than with the rice diet. Nitrogen balance studies were not done. Our studies have demon-

strated that, under hospital conditions, this diet may be used for prolonged maintenance of clinical improvement when initial treatment with the Kempner rice diet is successful.

As a regimen for treatment of hypertensive patients at home the special low-sodium diet is not entirely satisfactory. Many of the foods are expensive and constant dietetic supervision is required to maintain the extremely low NaCl intake. As mentioned previously, a very limited experience with this diet in outpatients has been only partially successful.

SUMMARY AND CONCLUSIONS

1. A four-year investigation of the Kempner rice regimen in the treatment of hypertension has been extended to determine the effects of adding NaCl, protein, fat and vegetables to the basic diet. These modifications have been studied separately and, with the exception of sodium chloride, also collectively in a specially devised low-sodium diet of approximately normal food composition. The experiments were conducted in a hospital environment under controlled conditions. Most of the forty-seven patients investigated were in advanced stages of hypertensive cardiovascular disease.

2. Addition of 3 gm. of NaCl per day to the rice diet from the time of its institution prevented any lowering of blood pressure. In patients who had shown a significant anti-hypertensive response to the rice or special low-sodium diets, the addition of 0.5 gm. of NaCl per day in tablet form usually did not elevate the blood pressure. Addition of larger amounts of NaCl usually did evoke significant rises in blood pressure.

3. In patients who had responded favorably to the unmodified regimen no loss of beneficial effects was noted when 12 to 50 gm. per day of low-sodium protein, 20 to 40 gm. per day of fat and 200 gm. per day of vegetables were added singly or together to the diet. Decreases in blood pressure similar to those obtained with the rice diet occurred in three patients who were given a special low-sodium diet without previous treatment with the Kempner regimen.

4. The results of these investigations bear out the initial impression that the effective anti-hypertensive principle of the rice diet is the restriction of sodium ion. The findings further suggest that in those patients with essential hypertension in whom beneficial effects of stringent NaCl deprivation have been obtained, clinical improvement may be preserved on a more liberal diet than the Kempner rice regimen. Thus a major obstacle to the dietary treatment of hypertension, namely, the patients' ultimate failure to continue the rigorous program, may be overcome.

Acknowledgments: We are grateful to many for assistance and advice rendered in the course of this study. We are particularly indebted to Drs. Seymour Dayton, Judith Nadell, Ernest Schmatolla, Nell Kuhn of the First Medical Division; Drs. Howard E. Wiener, Royal Howard, Paul Stillman, Maurice Rubin, Nadhim Zilka, Norman Yourish of the Department of Ophthalmology and Dr. Henry K. Taylor of the Department of Radiology.

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Hyperlipoproteinemia*

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THE transport of the lipids of the blood via a series or "spectrum" of lipoproteins measurable ultracentrifugally has been described.[1-3] Significant aberrations in the serum lipoproteins have been described for coronary heart disease,[4,5] in diabetes,[6,7] infectious hepatitis[8] and infectious mononucleosis.[9] Of special interest are several clinical entities which are characterized by grossly abnormal serum concentrations of one or another of the ultracentrifugally defined lipoprotein classes. Certain aspects of lipoprotein findings in these states have been previously reported.[10] In part such entities are of intrinsic interest; in part they are of interest for the light they may shed upon the factors responsible for the variability in the serum levels of the various lipoproteins in the population at large. In this discussion particular consideration will be given to the following entities: xanthoma tendinosum, xanthoma tuberosum, xanthelasma, nephrotic syndrome, biliary obstruction, myxedema and "essential hyperlipemia." The lipoprotein classes to be considered are those designated as the standard S_f0–12, standard S_f12–20, standard S_f20–100 and standard S_f100–400 lipoproteins. The detailed methodology for the quantitative analysis of these lipoprotein classes in human serum is described elsewhere.[11] The mean levels and a measure of their variability for overtly healthy individuals of both sexes up to age seventy years are available for comparison with the specific disease entities to be considered here.[12]

TABLE 1
SERUM LIPOPROTEIN CONCENTRATIONS IN EIGHTEEN PATIENTS WITH XANTHOMA TENDINOSUM LESIONS

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1*	F	51	1091	195	152	29
2	F	14	918	224	204	60
3†	F	51	1037	372	396	72
4	F	52	1196	96	81	4
5	M	27	547	49	49	13
6	F	34	482	130	54	11
7	M	50	688	155	114	34
8	M	48	972	170	114	0
9	M	39	544	83	92	60
10	M	27	822	141	141	67
11	M	41	542	87	65	9
12	F	52	842	170	132	58
13	M	33	943	69	114	49
14‡	M	46	715	157	116	7
15‡	M	41	795	233	137	49
16‡	M	43	775	204	204	85
17	F	16	1120	58	36	7
18	M	39	452	110	103	31
Mean lipoprotein levels for xanthoma tendinosum			793	150	128	36
Mean lipoprotein levels for matched control series			336	65	92	56
Difference in mean levels in standard score units			+5.3	+3.1	+0.8	−0.4

* This patient showed a diffuse palmar planar skin lesion in addition to xanthoma of the tendons.

† This patient showed xanthelasma of the eyelids in addition to xanthoma tendinosum.

‡ Each of these patients showed extensive involvement with tendinous xanthomas plus a skin lesion.

Xanthoma Tendinosum. A group of eighteen patients with xanthomatous lesions involving the tendons was studied. Some of these patients reported that some of their lesions had been present since childhood. The individual lipoprotein results for the entire series of patients with xanthoma tendinosum are presented in Table 1. For purposes of comparison of the levels in xanthoma tendinosum with clinically healthy individuals, a synthetic control series matched by age and sex was prepared from a large series of random clinically healthy individuals.[12] A useful approach to consideration of the extent of difference of the individual lipoprotein levels between patients with xanthoma tendinosum and the matched control group is that utilizing

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standard scores. The standard scores of difference in means between the disease and the matched control population is equal to the difference in means divided by the standard deviation of the measurement. The values are presented in Table I. In xanthoma tendinosum the increase in lipoprotein level is greatest in the standard S_f0–12 lipoproteins, next in the standard S_f12–20 lipoproteins and least in the standard S_f20–100 lipoproteins. The standard S_f100–400 lipoprotein level is slightly but significantly lower in xanthoma tendinosum than in matched controls.

TABLE II

SERUM LIPOPROTEIN CONCENTRATIONS IN TWENTY-THREE PATIENTS WITH XANTHOMA TUBEROSUM LESIONS

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1	M	54	237	132	576	952
2*	F	60	164	128	1832	2804
3	M	38	253	130	479	258
4	F	54	134	114	504	500
5	M	46	179	123	813	668
6	M	44	105	74	531	90
7	M	27	291	134	314	74
8	F	54	224	155	650	352
9	M	57	228	119	697	1219
10	M	44	267	170	502	280
11	M	42	172	76	634	2283
12	M	33	159	130	529	226
13	M	32	159	103	665	786
14	M	34	152	121	428	500
15	M	33	403	172	706	515
16	M	47	132	87	448	475
17	F	44	143	121	403	340
18	M	42	172	99	452	220
19	F	53	141	130	558	329
20	M	45	222	116	524	766
21	M	31	233	134	549	444
22	M	59	199	110	562	524
23*	F	51	332	242	804	361
Mean lipoprotein levels in xanthoma tuberosum			206	128	616	650
Mean lipoprotein levels for matched control series			358	74	105	72
Difference in mean levels in standard score units			−1.9	+1.8	+9.1	+7.9

* These two patients showed a rare tendinous lesion on the extensor tendons of the fingers in addition to extensive lesions of the tuberous variety in the various characteristic skin sites.

Xanthoma Tuberosum. A group of twenty-three patients with xanthomatous lesions of the skin was studied. Characteristic sites of the lesions in this group were (1) extensor surfaces of elbows, (2) buttocks, (3) extensor aspect of knees, (4) hands, especially volar surfaces, (5) over ankle malleoli, especially laterally. In contrast to the patients with xanthoma tendinosum, none of the patients with xanthoma tuberosum reported the presence of lesions in childhood. The individual lipoprotein results for the entire series of patients with xanthoma tuberosum are presented in Table II, with matched clinically healthy controls selected as described. In xanthoma tuberosum the increase in lipoprotein levels is greatest in the standard S_f20–100 lipoproteins and in the standard S_f100–400 lipoproteins. The standard S_f12–20 lipoprotein level is significantly increased but to a

TABLE III

SERUM LIPOPROTEIN CONCENTRATIONS IN FORTY-THREE PATIENTS WITH XANTHELASMA

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1	M	47	410	204	155	67
2	F	70	300	67	56	29
3	F	61	417	155	251	103
4	M	68	392	139	108	47
5	F	58	284	273	125	136
6	F	46	484	81	148	164
7	F	57	423	67	56	22
8	F	47	332	40	40	25
9	F	52	426	130	146	119
10	M	53	493	83	112	47
11	F	63	464	101	74	29
12	F	69	495	85	43	9
13	F	40	309	36	54	20
14	F	37	466	56	60	27
15	F	54	349	60	36	22
16	F	48	578	101	119	43
17	M	37	600	128	184	36
18	F	70	370	244	99	20
19	F	53	979	92	188	119
20	M	41	538	130	143	67
21	F	48	450	87	38	22
22	F	48	367	40	43	16
23	F	38	347	65	267	108
24	M	39	459	94	157	114
25	M	45	363	65	112	121
26	F	56	258	405	231	29
27	F	45	491	141	101	36
28	F	35	524	74	65	38
29	F	33	475	166	110	22
30	F	47	455	157	45	9
31	F	50	511	179	74	36
32	F	45	403	40	63	16
33	F	51	475	99	87	7
34	F	49	417	96	119	146
35	M	35	300	60	65	38
36	M	63	455	112	58	11
37	F	60	417	92	130	179
38	M	60	513	74	65	52
39	F	53	426	105	87	38
40	M	50	520	82	103	52
41	F	47	392	67	69	25
42	F	42	491	105	137	105
43	F	45	500	105	114	76
Mean lipoprotein levels for xanthelasma			444	112	105	54
Mean lipoprotein levels for matched control series			352	76	96	54
Difference in mean levels in standard score units			+1.1	+1.2	+0.2	0

much lesser extent than the standard S_f20–100 or standard S_f100–400 lipoprotein classes. However, the standard S_f0–12 lipoprotein level is significantly lower than in the matched controls.

Xanthelasma. A group of forty-three patients with xanthelasma* (xanthoma palpebrarum) was studied. These patients represent a group referred for study because of xanthelasma rather than for such diseases as coronary heart disease, which did co-exist in some cases. None of these patients had any of the other disease states discussed in this report. Epstein[13] has previously reported lipoprotein and cholesterol data for xanthelasma patients so selected. The individual lipoprotein results for this series of patients are presented in Table III. In xanthelasma an increase in lipoprotein levels is noted in both the standard S_f0–12 and standard S_f12–20 classes. The extent of lipoprotein level elevation above the matched control series is essentially the same (on a standard score basis) for the standard S_f0–12 and standard S_f12–20 classes. Xanthelasma patients show no significant lipoprotein deviations from those in matched controls either in the standard S_f20–100 or standard S_f100–400 classes.

TABLE IV
SERUM LIPOPROTEIN CONCENTRATIONS IN THIRTEEN PATIENTS WITH THE NEPHROTIC SYNDROME

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1	M	3	629	199	656	600
2	M	6	455	139	728	748
3	M	6	961	296	549	235
4	M	5	1290	345	1219	710
5	F	4	856	253	316	83
6	M	4	571	193	585	435
7	M	3	692	177	222	37
8	F	3	461	199	591	459
9	M	4	567	177	318	255
10	M	4	1212	340	627	345
11	F	6	862	269	558	112
12	M	41	511	85	213	110
13	M	27	1158	401	992	493
Mean lipoprotein levels for nephrotics (mg. %)			787	236	583	355
Mean lipoprotein levels for matched control series (mg. %)			276	41	69	37
Difference in mean levels in standard score units.			+6.3	+9.8	+14.7	+11.0

* Many of the xanthelasma cases in this group are members of a series of patients under study by Epstein, Rosenman and Gofman for the relationship of xanthelasma to atherosclerosis.

Nephrotic State. A group of thirteen patients with the typical clinical picture of the active nephrotic syndrome was studied. The individual lipoprotein results for this series of patients are presented in Table IV. In the nephrotic state the mean levels of all four lipoprotein classes are extremely elevated.

TABLE V
SERUM LIPOPROTEIN CONCENTRATIONS IN SIX PATIENTS WITH CHRONIC BILIARY OBSTRUCTION

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1*	F	52	773	627	157	0
2†	M	33	898	659	150	11
3†	F	46	1550	2119	3472	78
4†	F	24	909	1512	2598	114
5	F	45	746	836	844	45
6*	F	40	579	575	372	49
Mean lipoprotein levels for biliary obstruction.			910	1053	1265	49
Mean lipoprotein levels for matched control series			346	70	78	39
Difference in mean levels in standard score units.			+7.0	+29.2	+29.7	+0.3

* These patients showed skin xanthoma.
† These patients showed eyelid and skin xanthomas.

Biliary Obstruction. A group of six patients presenting the typical clinical features of chronic biliary obstruction, with or without xanthomatosis, was studied. The etiology of the biliary obstruction in several of these cases remained obscure in spite of investigation, including laparotomy. The lipoprotein findings in the six cases of chronic biliary obstruction are presented in Table V. In biliary obstruction massive elevations are the rule in the levels of standard S_f0–12 and standard S_f12–20 lipoproteins. The standard S_f20–100 lipoprotein level may or may not be grossly elevated. The standard S_f100–400 lipoproteins show a mean level not differing significantly from that in clinically healthy individuals. Chemical and physicochemical studies of the lipoproteins in biliary obstruction, to be reported elsewhere, show that certain classes of lipoproteins in this disease differ from those encountered in other states, even though their flotation rates under the conditions employed in these studies are similar.

Myxedema. Only two untreated patients with spontaneous myxedema were available for lipoprotein study. The lipoprotein findings in these two cases are presented in Table VI.

Even with the paucity of cases it is demonstrable that the standard S_f0–12 and standard S_f12–20 lipoprotein levels are markedly elevated in spontaneous myxedema. No significant difference in the standard S_f20–100 and standard S_f100–400 lipoprotein levels between the myxedema cases and the matched controls was observed.

"*Essential Hyperlipemia.*" There exists a vaguely defined clinical state diagnosed as "essential" or "idiopathic" hyperlipemia, usually discovered by the incidental finding of creamy serum in a fasting blood specimen. Manifestly, the criteria for such a diagnosis can hardly be regarded as quantitative or definitive. Some authors[14] refer to xanthoma tuberosum as "essential hyperlipemia" in those patients with xanthoma tuberosum in whom the fasting serum appears creamy. In our considerations reference is made only to patients referred for study because of creamy serum but who do not show any visible xanthomatous lesions. Nine such patients were available for lipoprotein analysis. The findings are presented in Table VII. In "essential hyperlipemia" the standard S_f100–400 lipoproteins show the greatest elevation in level as compared with matched controls, and in addition there is a great elevation in the standard S_f20–100 lipoprotein level. The standard S_f12–20 lipoprotein class is not significantly different in level from that for the matched control group. The standard S_f0–12 lipoprotein level is significantly and markedly lower than that in the matched control group.

Comments. It is evident that the several disorders herein described represent entities which may differ strikingly in the pattern of serum lipoprotein transport. It would appear from Figure 1 that the differential diagnosis of several of these conditions can be made from the lipoprotein analysis alone. The level of the standard S_f0–12 lipoproteins separates "essential hyperlipemia" and xanthoma tuberosum from the other five conditions described. These two diseases are easily differentiated from normals by the level of the standard S_f20–100 or standard S_f100–400 lipoproteins. The distinction between "essential hyperlipemia" and xanthoma tuberosum cannot always be made with certainty from the lipoprotein analysis alone but, generally speaking, xanthoma tuberosum is characterized by higher levels of the standard S_f20–100 lipoproteins than the standard S_f100–400 lipoproteins while the reverse is true in "essential hyperlipemia." Of the five diseases which have marked elevations of the levels of standard S_f0–12 lipoproteins, biliary obstruction can be differentiated on the basis of a high level of standard S_f12–20 lipoproteins, higher than is seen in any other condition, and very low levels of the standard S_f100–400 lipoproteins. In biliary obstruction the contour of the lipoprotein spectrum is so distinctive that even without actual measurement of the milligram per cent levels of the various lipoprotein classes the diagnosis can hardly ever, if ever, be missed. This characteristic contour has been shown elsewhere.[10] Of the four remaining conditions, the nephrotic syndrome is distinguished from xanthoma tendinosum, xan-

TABLE VI

SERUM LIPOPROTEIN CONCENTRATIONS IN TWO PATIENTS WITH SPONTANEOUS MYXEDEMA

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1	F	60	827	193	103	16
2	F	44	730	130	112	18
Mean lipoprotein levels for the two cases of myxedema			779	161	107	17
Mean lipoproteins for matched control group			363	90	99	52
Difference in mean levels in standard score units.			+5.3	+1.4	+0.2	−0.8

TABLE VII

SERUM LIPOPROTEIN CONCENTRATIONS IN NINE PATIENTS WITH "ESSENTIAL HYPERLIPEMIA"

Case No.	Sex	Age (yr.)	Concentration in mg. %			
			Standard S_f0–12	Standard S_f12–20	Standard S_f20–100	Standard S_f100–400
1	M	29	228	60	289	504
2	M	49	130	38	517	959
3	F	50	184	76	450	1483
4	F	68	280	92	1100	2937
5	M	44	202	92	493	627
6	M	47	211	81	482	822
7	M	35	264	18	244	676
8	M	43	242	83	291	560
9	M	37	320	58	184	132
Mean lipoprotein levels in "essential hyperlipemia"			229	66	450	967
Mean lipoprotein levels in matched controls			364	68	109	83
Difference in mean levels in standard score units.			−1.6	−0.1	+7.1	+11.5

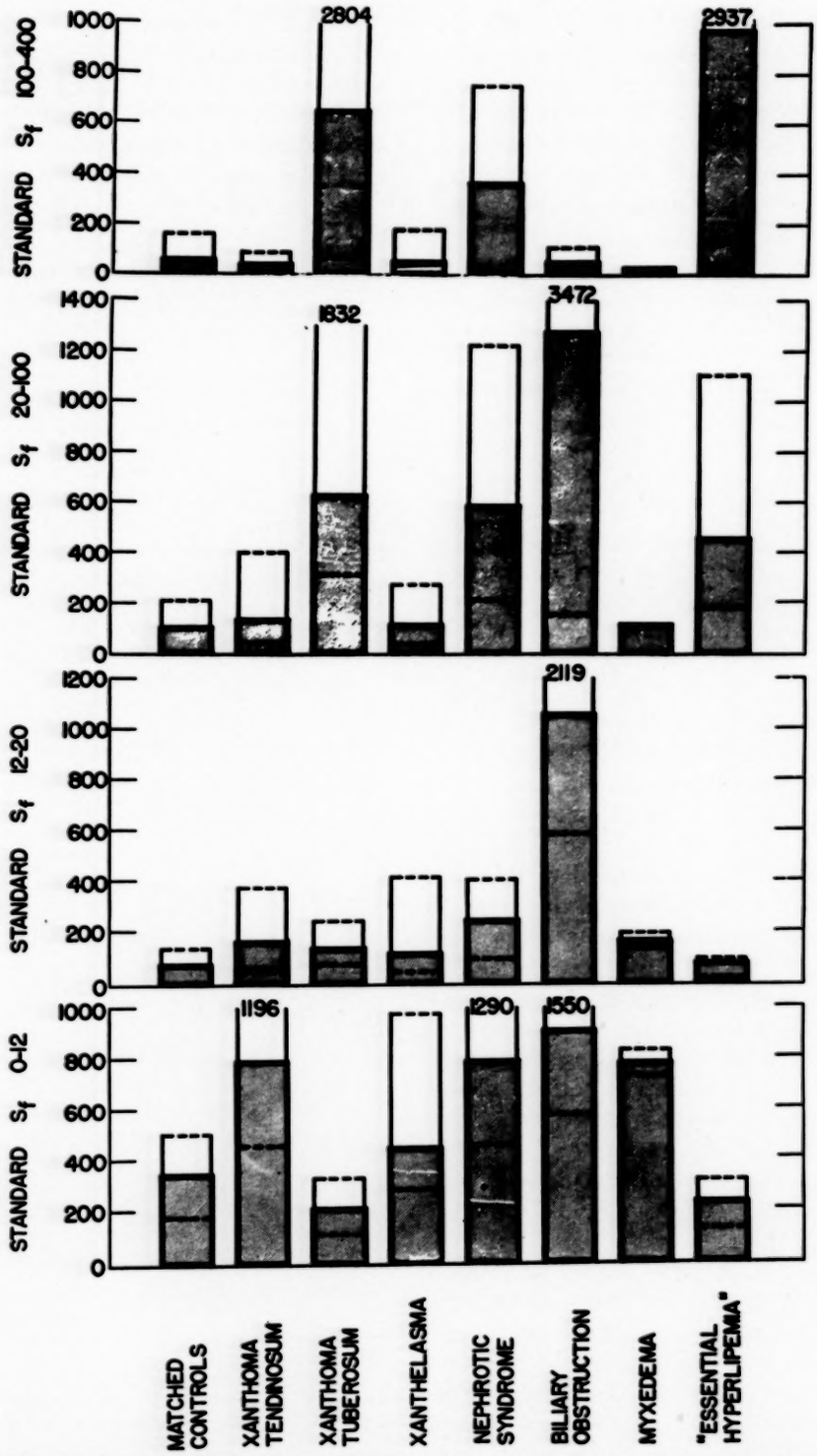

FIG. 1. The mean levels of serum lipoprotein concentration in the various disease states and a control group matched for age and sex for the four lipoprotein classes are shown by the hatched areas. The entire ranges of values found in the patients described here are shown by the interrupted lines. In some disease categories the highest level of lipoproteins found was off the scale of the graph; these high values are written in the appropriate space. For the matched control group the interrupted lines show the levels at two standard deviations from the control mean values.

thelasma and myxedema by higher levels of the standard S_f20–100 and standard S_f100–400 lipoproteins. These three remaining diseases may have very similar serum lipoproteins although in xanthelasma the level of the standard S_f0–12 is in general considerably lower than that of the other two entities. It is quite possible that similar metabolic defects are operative in xanthoma tendinosum, xanthelasma and myxedema.

The data presented here reveal several additional interesting facts which probably bear on the etiology of some of the hyperlipoproteinemias. The age-sex distribution of cases of xanthoma tuberosum (Table II) shows that in this series fourteen of the seventeen males were under the age of fifty, while five of the six females were over the age of fifty. A (x)chi^2 test indicates that this could occur by chance alone in less than one in a hundred times. It is significant therefore that in males xanthoma tuberosum develops at a much younger age than in females.

It is of interest that for the xanthoma tendinosum, xanthoma tuberosum and "essential hyperlipemia" types of lipoprotein transport disturbances, we have evidence that a familial factor may operate.

In xanthoma tendinosum two types of evidence of the familial factor are available. The father, a paternal uncle, and a brother of Case 7 (Table I) were reported in the literature to show xanthomatosis.[15] The title of that report is "Xanthoma Tuberosum," although the photographs shown indicate clearly that the actual lesions were of the tendinous variety. Another type of evidence is shown by a nineteen year old daughter of Case 3 (Table I) who demonstrates no xanthomatous lesions upon examination, although her lipoprotein findings are characteristic of those found in xanthoma tendinosum. The actual lipoprotein levels in this relative of a case of xanthoma tendinosum are the following:

Standard S_f0–12	= 793 mg. %
Standard S_f12–20	= 114 mg. %
Standard S_f20–100	= 54 mg. %
Standard S_f100–400	= 4 mg. %

The standard S_f0–12 lipoprotein is approximately seven standard deviations above the mean for females of her age which makes it extremely unlikely for the observed result to be a chance occurrence.

In xanthoma tuberosum the familial factor is evidenced by the observations on Cases 1 and 8, who are siblings, and show classic xanthoma tuberosum lesions.

In "essential hyperlipemia" the familial factor is evident from the fact that Cases 5 and 6 (Table VII) are brothers.

Although the single examples given for each of the lipoprotein disturbances in which a familial factor may be operating are sufficient for the purposes of statistical significance, many additional examples are available. For each lipoprotein abnormality the evidence to date indicates that the abnormality of serum lipoproteins shown by a relative is of the same type as is present in the index case. Other investigators[16–18] have reported the existence of familial factors from studies of the occurrence of xanthomatous lesions and of hypercholesterolemia.

Serum cholesterol levels, comparably elevated in many of the patients with any of these disorders, will not afford differentiation among the various types. Turbidity of the fasting serum can lead to erroneous conclusions regarding the differential diagnosis of these metabolic defects. On this basis Lever[19] has recently grouped all cases of "essential" hyperlipemia and xanthoma tuberosum in one class called idiopathic hyperlipemia and referred to cases of xanthoma tendinosum as primary hypercholesteremic xanthomatosis even though the mean cholesterol level in this latter condition was lower than the cholesterol level of the idiopathic hyperlipemia group. A very small increase in the concentration of the very large lipoproteins can give rise to turbidity even in cases of xanthoma tendinosum. Similarly patients with xanthoma tuberosum who have most of their lipoproteins in the standard S_f20–100 class and only small concentrations of the standard S_f100–400 class of lipoproteins may have very clear sera. Although an occasional patient may have both tendinous and tuberous xanthomas, the vast majority of patients have 95 per cent of their lesions belonging to one category or the other, but not both. Many xanthoma tuberosum patients have a single small tendinous lesion in the extensor tendor of one finger. It is believed that no system of nomenclature should include both forms of xanthoma in one or all diagnostic classes especially inasmuch as there are such definite differences which can be detected by physical means.

The specificity of the relationship of localization of xanthomatous lesions to the type of lipoprotein molecules present at elevated levels is

of great interest, although the mechanism of this specificity is not clear at present.

SUMMARY

1. The serum lipoproteins of cases of xanthoma tendinosum, xanthoma tuberosum, xanthelasma, the nephrotic syndrome, biliary cirrhosis, myxedema and "essential" hyperlipemia are compared with each other and with the normal serum lipoprotein distribution.

2. The diagnosis of the nephrotic syndrome can almost always be made by the serum lipoprotein spectrum alone.

3. The diagnosis of biliary cirrhosis can almost always be made by the serum lipoprotein spectrum alone.

4. Xanthoma tuberosum and "essential" hyperlipemia can almost always be differentiated from the other conditions by means of the serum lipoproteins alone and usually patients with these conditions can be differentiated from each other by this test.

5. Xanthoma tendinosum, xanthelasma and myxedema can be distinguished from the other conditions described here but the serum lipoprotein spectra in these cases are sufficiently similar to each other to make it difficult or impossible to make the differential diagnosis among them by the serum lipoproteins alone.

6. It is suggested that the serum lipoprotein spectrum be considered the standard diagnostic feature of these illnesses rather than such nebulous criteria as turbidity of sera, or such non-distinguishing criteria as serum cholesterol determinations.

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The Serum Lipoproteins in Infectious Mononucleosis*

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REPORTS of the past few years have shown that hepatic involvement is clearly evident in the vast majority of cases of infectious mononucleosis.[1-33] More recently it has been revealed that various abnormalities of the liver are accompanied by variations in serum lipoprotein distribution and concentration. This is not surprising inasmuch as the liver plays a major role in both lipid and protein metabolism. In 1952 McGinley, Jones and Gofman[34] reported that biliary cirrhosis in humans was characterized by a specific serum lipoprotein spectrum consisting of two major components, one at S_f8 and the other at S_f13, with essentially no lipoproteins of the class of S_f20 or higher. More recently Pierce[35] reported serum lipoprotein changes in infectious and serum hepatitis. Still different serum lipoprotein patterns have been established for various experimentally induced pathologic states of the liver, such as carbon tetrachloride poisoning,[36] alloxan intoxication[37] and ethionine administration.[38] In view of the specificity of some of these changes it seemed advisable to investigate the serum lipoproteins in infectious mononucleosis.

METHODS

Cases were collected from the Cowell Memorial Hospital at the University of California in Berkeley. All subjects were hospitalized and all were students at the university. In order to get blood samples as early as possible in the disease, all cases admitted with a provisional diagnosis of infectious mononucleosis were studied. Cases were collected during a three-month period from March to June, 1952. Periodic follow-up was attempted in all cases for one year. To obviate subjectivity in collection and grouping of cases, the final diagnosis on the hospital chart was the sole determining factor in deciding whether or not a case should be considered one of infectious mononucleosis; this diagnosis was made by a member of the hospital staff who had no information concerning the results of the serum lipoprotein measurements. The diagnosis of infectious mononucleosis was based on the usual laboratory and clinical findings. Heterophil agglutination tests were carried out in all patients but the specific absorption tests of Davidsohn[39] with guinea pig kidney and ox red blood cells were not in use at the hospital at this time. The control group consisted of those cases which did not have a final diagnosis of infectious mononucleosis. This group included cases of tuberculosis, virus pneumonia, bronchitis, acute fatigue, pharyngolaryngitis and rubella. Cases in the following categories were excluded completely from the study: those diagnosed as infectious hepatitis or having a thymol turbidity of 5.5 units or over without a final diagnosis of infectious mononucleosis; those with a diagnosis of probable infectious mononucleosis; and, because of the major changes in serum lipoproteins which occur with age, those over thirty-five years of age. Table 1 shows the composition of the groups used in this study.

Serum lipoproteins were determined by the ultracentrifugal method of de Lalla and Gofman.[40] Low density lipoproteins are those lipoproteins less dense than 1.050. These have been divided into four groups according to flotation rate: standard S_f0–12, standard S_f-12–20, standard S_f20–100 and standard S_f100–400. The term "standard" signifies that the mg. per cent values have been corrected for the effects of concentration on flotation rate.[41] In general, there were no significant concentrations

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of lipoproteins with rates faster than S_f400 in these patients. High density lipoproteins were divided into two groups, those of density between 1.125 and 1.063, the L lipoproteins, and those of density between 1.125 and 1.199, the T lipoproteins. The L and T lipoproteins are the same lipoproteins which have been called HDL_2 and HDL_3, respectively, elsewhere.[40]

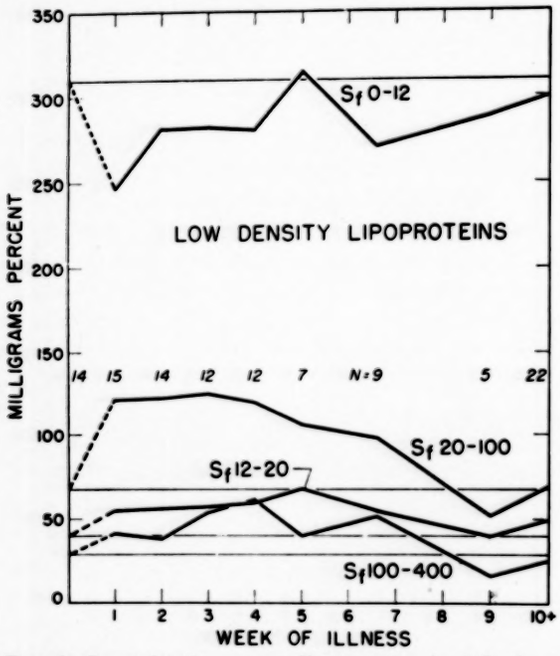

FIG. 1. Low density serum lipoproteins in infectious mononucleosis. The horizontal solid lines show the mean level in a group of controls. N is the number of cases at each point. The first N, 14, refers to the control group.

RESULTS

The results in males are shown graphically in Figures 1 to 4. The week of illness, plotted on the abscissa, is calculated from the first symptom mentioned in the history in the hospital chart. Such an arbitrary decision is necessary in a disease such as this. The horizontal solid lines show the mean values for the male control group and is joined to the curve of the mean values for the infectious mononucleosis group by the dotted line. The number of determinations represented by any point in the curve is shown by N. The first N, 14, refers to the control group. The points plotted at 10+ weeks include all samples drawn between the tenth week of illness and one year after onset of the infection.

The four groups of low density lipoproteins are shown in Figure 1. It is seen that the concentration of the standard S_f0–12 class was below normal early in the disease and increased to normal levels as the illness and then recuperation progressed. The increase seen in this class of lipoproteins between the first and second to fourth weeks of illness, although not of great magnitude, is significant at the 5 per cent level. All determinations of the standard S_f0–12 class after the fifth week are different from those of the first week at the one per cent level of significance. The change observed in the standard S_f12–20 class of lipoproteins throughout the course of the infection and during convalescence was an increased concentration at the 5 per cent level of significance. Both the standard S_f20–100 and S_f100–400 classes of serum lipoproteins were significantly elevated in concentration at the start of the illness and did not start to fall to normal levels until several weeks had passed. By the ninth week after the onset of symptoms essentially normal levels were present in all four groups.

TABLE I*

Group	Sex	No. of Patients	No. of Determinations	
			Low Density	High Density
Infections mononucleosis	M	28	96	46
	F	8	31	18
Control	M	8	14	9
	F	6	9	5

* Constitution of the groups of patients used in this study and the number of serum lipoprotein determinations made in each group.

The high density lipoproteins, shown in Figure 2, revealed the changes of greatest statistical significance, the T lipoprotein being especially significant. These were depressed below normal during the first seven weeks of the illness. By the ninth week normal levels were established.

Table II shows the significance of all changes observed. It is interesting to note that for all six classes of lipoproteins measured the values ten weeks or more after the onset of symptoms did not differ appreciably from those found in the control group, nor do they differ from the normal values found in a large series of normal males of this age group.[42] The mean age of the male con-

trol group was 20.3; the mean age of the male infectious mononucleosis group was 22.4. The results in females with infectious mononucleosis revealed changes of the same kind and magnitude as in males with the exception that the change in the high density classes was even more striking. The results in males and females were not pooled because of the different levels of lipoproteins which occur normally in the two sexes.

TABLE II*

Week of Illness	S_f Class	Mean (mg. %)	Standard Error	t	p
1	0–12	246	9.6	....	.....
2–4	0–12	281	13.	2.17	0.05
5+	0–12	295	11.	3.36	0.01
1–8	12–20	58	2.4	....	.....
9+	12–20	48	3.9	2.17	0.05
1–8	20–100	116	5.5	....	.....
9+	20–100	67	6.7	5.6	<0.001
1–8	100–400	48	4.5	....	.....
9+	100–400	24	3.5	4.2	<0.001
1–8	High density L	28	3.5	....	.....
9+	High density L	53	5.7	3.7	0.001
1–8	High density T	123	6.5	....	.....
9+	High density T	192	8.5	6.4	<0.001

* The mean changes which occurred in the six groups of serum lipoproteins measured and the probability that these changes occurred by chance alone.

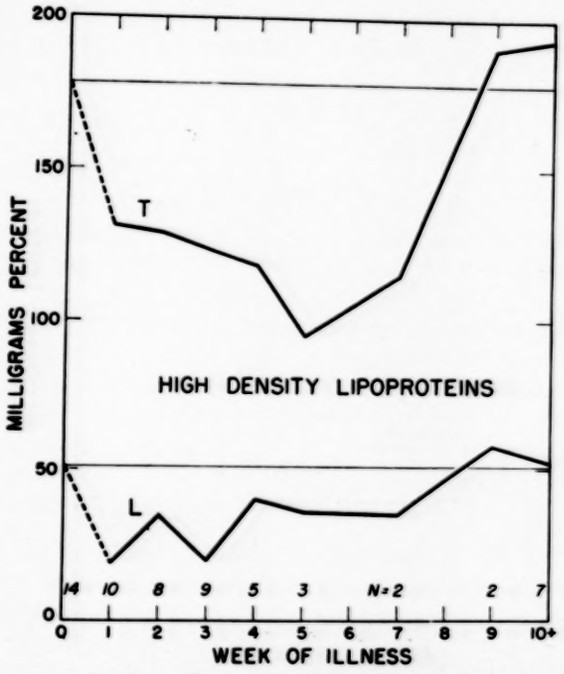

FIG. 2. High density serum lipoproteins in infectious mononucleosis. The horizontal solid lines show the mean level in a group of controls. N is the number of cases at each point. The first N, 14, refers to the control group.

COMMENTS

The changes observed during the course of infectious mononucleosis can be summarized by stating that the concentration of all lipoproteins with flotation rates less than S_f12 was decreased during the illness while the concentration of all lipoproteins with flotation rates greater than S_f12 was elevated during the course of the disease. This is shown in Figure 3. The concentrations of all classes of lipoproteins ten weeks or more after the onset of the illness were not different from those found in a control group.

It has been suggested that the pathologic process in infectious hepatitis is very similar to that in infectious mononucleosis.[3,5,8,23,43,44] Wadsworth[25] points out that the most diagnostic feature of the liver in infectious hepatitis, the great variation seen from cell to cell, is also found in infectious mononucleosis. When jaundice starts at the onset of infectious mononucleosis, there is nothing to distinguish the clinical condition from infectious hepatitis.[7,45–48] It has even been postulated that jaundice in infectious mononucleosis may be caused by the same virus as in infectious hepatitis.[26,45,46] Many investigators have shown that there are other similarities between infectious hepatitis and infectious mononucleosis.[48] A decrease in albumin and an increase in alpha, beta and gamma globulin may occur in both conditions.[3,7] The abnormal lymphocytes once thought to be characteristic of infectious mononucleosis may also be found in infectious hepatitis.[8,43]

In spite of the similarity between the usual clinical tests of liver function in infectious hepatitis and infectious mononucleosis, and in spite of the similarity of the pathologic findings in the liver both at autopsy and by biopsy,[23,26,43] the diseases are generally believed to be different. The main difference, of course, is the presence of heterophil antibody in infectious mononucleosis,[39] however, it has been reported to be present in infectious hepatitis.[43] Another difference between the infections is the relatively small number of cases of infectious mononucleosis which become clinically jaundiced from 0 to 13 per cent.[3,5,8,21,22,26,33,48]

The data presented here may now be added to that list of information which indicates that the processes are different. Pierce[35] reported on the changes occurring in the low density group of serum lipoproteins in infectious and serum hepatitis and found that the concentrations of

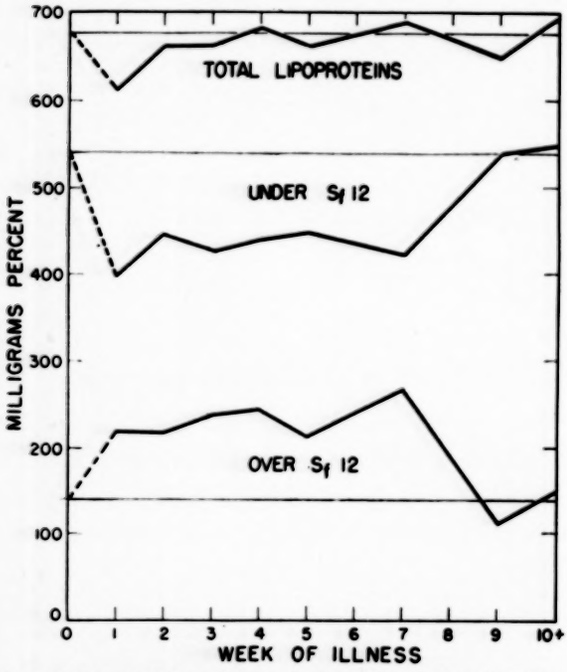

FIG. 3. Total high and low density lipoproteins in infectious mononucleosis. The horizontal solid lines show the mean levels in a control group.

the standard S_f0–12, S_f12–20 and S_f20–100 classes were all elevated and that the standard S_f100–400 class was significantly decreased. This is in marked distinction to the data presented here. de Lalla[49] found that the high density serum lipoproteins in infectious hepatitis are markedly decreased in concentration, as they are in infectious mononucleosis.

Inasmuch as so many systems can be involved in this disease, the skin, mucous membranes, peripheral and central nervous system, heart, lungs, marrow, kidney, etc.,[15,17,26,46,47,48,50–57] it is possible that the serum lipoprotein changes are caused by aberrations of some organ other than the liver. In view of the fact that the mesenchymal reaction in both infectious mononucleosis and infectious hepatitis predominates, it certainly seems that these diseases are not specifically diseases of the liver but rather primarily involve the reticulo-endothelial system.[11,58] Because of the known role of the liver in the intermediary metabolism of lipids and proteins, it seems reasonable at this time to associate the changes in serum lipoproteins in infectious mononucleosis and infectious hepatitis with the hepatic changes which occur in these diseases, whether this be primary or secondary to reticulo-endothelial changes.

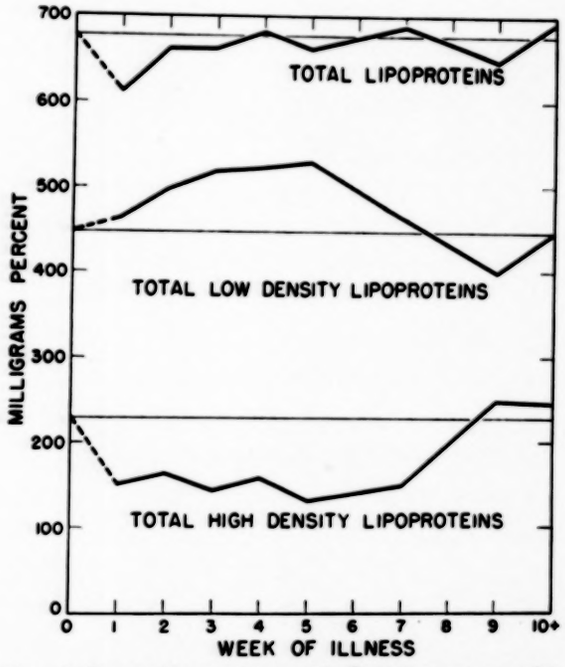

FIG. 4. Serum lipoproteins with flotation rates under and over S_f12 during infectious mononucleosis. The group of lipoproteins designated "under S_f12" includes the S_f0–12 class as well as both of the high density lipoprotein classes.

Several of the flocculation tests which are used as tests of liver function, such as the cephalin-cholesterol flocculation test and the thymol turbidity test, appear to be dependent in some way on lipid. Even though the cephalin-cholesterol flocculation test can be performed with lipid-free serum,[59] the addition of the cephalin-cholesterol emulsion itself may well provide the lipid needed for the test.[60] Since the thymol turbidity test correlates well with the gamma globulin level late in hepatitis,[60] the lipid in this case may also be a non-specific indicator.[61] It has been postulated[60,61] that a redistribution of the lipoprotein is the basis for these tests. Pierce's data[35] and the data presented here indicate that a redistribution of the low density lipoproteins, as shown by ultracentrifugal analysis, is not the basis for these flocculation tests. Pierce[35] was unable to find any correlation between the thymol turbidity test and

any of the four groups of low density lipoproteins in infectious hepatitis. The present data add confirmation to this lack of correlation. Seventy-five per cent of infectious hepatitis cases and 73.5 per cent of infectious mononucleosis cases have positive thymol turbidity tests.[19] The fact that the standard S_f0–12 and standard S_f-100–400 classes of lipoproteins change in opposite directions in these two conditions supports the lack of correlation between these two classes of lipoproteins and the thymol turbidity test. Since the standard S_f12–20 class of lipoproteins remains essentially constant in infectious mononucleosis, one would expect to find no correlation between this class and the thymol turbidity test. Pierce[35] was able to show a correlation at the 5 per cent level of significance between the total low density group of lipoproteins and the thymol turbidity. In infectious mononucleosis there is also a rise in total low density lipoproteins. (Figure 4.) This again indicates that in the flocculation tests the lipid may be a non-specific indicator of a change which is occurring in some other protein fraction.

With regard to the cephalin-cholesterol flocculation test, Hanger[63] has shown that there are sufficient amounts of stabilizing factor present in normal serum to inhibit this flocculation. This factor has been identified as a labile, lipid-rich component of the electrophoretically derived albumin + alpha-1-globulin fraction.[63] It is quite possible that this factor is, or is contained in, the high density lipoprotein class since this class of lipoproteins is depressed markedly in both infectious mononucleosis and infectious hepatitis.

Most reports[1,3,8,33] indicate that the vast majority of cases of infectious mononucleosis have a normal fraction of the serum cholesterol in the esterified form. An occasional case has been reported to have a decreased amount of esterified cholesterol in serum.[21,64] From an analysis of the serum lipoproteins alone one would have expected a fall in the per cent esterified cholesterol in infectious mononucleosis since the high density and the S_f0–12 classes of lipoproteins are richest of all lipoproteins in esterified cholesterol, and these classes are the ones which are decreased in concentration.[65] The explanation probably will come about by chemical analyses of isolated classes of lipoproteins in infectious mononucleosis which may reveal that the chemical constitution of any class of lipoproteins found in infectious mononucleosis is different from that same class found in the population at large.

SUMMARY

1. The serum lipoproteins of twenty-eight male and eight female patients with infectious mononucleosis were studied during the course of the illness and for one year thereafter. Fourteen patients with various other illnesses were studied as controls.

2. Significant reductions in both high density lipoprotein fractions and the standard S_f0–12 class of lipoproteins were present during the course of the illness. Significant elevations of the standard S_f20–100 and S_f100–400 classes of lipoproteins were present during the course of the illness. The S_f12–20 class of lipoproteins was elevated only to the 5 per cent level of significance.

3. By the ninth week after onset of symptoms essentially normal levels of all serum lipoproteins were present.

4. The marked differences between the serum lipoproteins in infectious mononucleosis and infectious hepatitis are discussed.

Acknowledgment: The author wishes to thank Dr. William G. Donald, Sr., University physician, University of California at Berkeley, for making available the clinical material used in this study. Many thanks are also due to Dr. John W. Gofman, Arthur Tamplin, Frank Glazier, Agnes de la Torre and the ultracentrifuge section of Donner Laboratory for valuable assistance in the compilation of the data and to Oliver de Lalla for making available the technic for analysis of high density lipoproteins prior to publication of this method.

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Reviews

Spontaneous Subarachnoid Hemorrhage

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REGARDLESS of isolated opinions to the contrary,[1] non-traumatic bleeding into the subarachnoid space is now recognized as a clearly defined pathologic entity with a striking group of symptoms, almost unmistakable clinical picture, characteristic spinal fluid findings and a decidedly guarded prognosis. Modern concept ascribes all such instances of massive effusion of blood into the subarachnoid space to rupture of "berry" or "miliary" aneurysms of the circle of Willis.[2] Examples of subarachnoid hemorrhage due to intracranial rheumatic aneurysms,[3] blood dyscrasias, neoplasms, lues, arteriosclerosis, liver diseases, etc., are relatively rare and unimportant causes of this syndrome.

The occurrence, development and course of berry intracranial aneurysms has been fully described by Richardson and Hyland,[4] Forbus[5] and many others.[6–9] Forbus believes that these aneurysms are probably acquired but arise as a result of focal weakness in the arterial walls due to a congenital muscularis defect and degeneration of the internal elastic membrane due to constant overstretching. The aneurysms vary in size from 1 to 5 mm. or more and are usually situated at the angle of a branching artery. The majority of them are located at bifurcations of the anterior communicating arteries of the circle of Willis but may and do occur anywhere in the branches of this anastomosis.

Microscopic sections of these aneurysms show either an abrupt loss of elastic tissue at the neck of the sac or a gradual disappearance of the internal elastica and media.[4] The wall of the sac itself is composed entirely of fibrous tissue. Frequent occurrence of small hemorrhages in aneurysmal walls suggests that leaking of blood from the sac and subarachnoid space probably takes place due to slow dissection of the aneurysm, and final weakening and rupture are brought about in this manner.

Slow oozing from an aneurysmal sac before rupture can occasionally be correlated with the clinical symptoms of severe headache, apprehension, vertigo, possibly nystagmus, stiff neck, nausea and vomiting. These symptoms persist for as long as six days before actual rupture and their true significance is likely to be overlooked. The slow dissection undoubtedly accounts for the clinical observation that violent physical exertion with resultant increase in arterial tension is by no means a constant precipitating cause of rupture.

Spontaneous subarachnoid hemorrhage probably accounts for from 1 to 2 per cent of all sudden or unexplained deaths. The bleeding takes place between the pia mater and arachnoid, almost always at the base of the brain. Obviously, then, subsequent events depend upon the size of the rupture plus the amount of blood getting into the subarachnoid space. If the bleeding is extensive, it may terminate in immediate death by exerting sufficient pressure on the brain stem to cause coneing of the medulla into the foramen magnum.

There is scarcely a syndrome in the realm of medicine which is more dramatic in its onset and development than that of spontaneous subarachnoid hemorrhage. The signs and symptoms as set down by Barker[10] are as follows: (1) Sudden onset often with a feeling as though something had snapped in the head and followed by severe occipital pain which later tends to become generalized; (2) nausea or vomiting almost immediately after onset; (3) within a few hours marked rigidity of the muscles of the neck with positive Kernig and Brudzinski signs; (4) on cautious lumbar puncture blood will be found evenly distributed throughout the fluid in each of three successive tubes. (Barker could have added that within twenty-four to forty-eight hours the spinal fluid becomes xanthochromic, which can easily be seen when the red blood cells are allowed to settle to the bottom of the tubes or after centrifuging.)

The author has had an opportunity to observe twenty-three instances of spontaneous subarachnoid hemorrhage occurring in twenty-one patients (one died of recurrence six months following the initial attack and a second died slightly less than one year after the first seizure) in the course of the past ten years. These cases exhibited all of the symptoms, signs and findings enumerated by Barker but study of these patients led to some observations worthy of comment, plus mortality figures which are somewhat lower than generally quoted, except when severe hypertensive cardiovascular disease was an important factor. In these instances the fatality is 80 per cent.

OBSERVATIONS

Age and Sex Distribution. In this series there were nine males and twelve females; the ages varied from seventeen to seventy-two, the average being forty-four. (Table 1.)

Mode of Onset. All but two of these patients were seen within twelve hours of onset; many of them within an hour; and of the ten who were able to talk, six of them stated that "something snapped at the base of my brain" or "something broke inside my head." Of the eleven who were unconscious from the time of hemorrhage, five died in coma without ever showing signs of reviving, while four of the remaining six also stated that something within the skull had "given away." Practically all of the patients had more or less mental confusion and, if able to converse at all, talked incoherently and had a certain wild, apprehensive, terrified look about them which is not easily forgotten. The pain at the base of the skull is so excruciating that many patients writhe about in bed screaming or pace the floor trying to compress the skull between the two hands. Nausea, vomiting, dizziness, blurred vision, drowsiness, stiff neck, pain and stiffness in the back radiating down the posterior aspect of the thighs and legs (a common symptom due to irritation of the dorsal nerve roots as the blood passes down the spinal fluid), convulsions, deepening stupor and finally coma may occur. Generalized convulsions were present in six of these patients but as noted by others[11] did not appear to be a determining prognostic sign as three of them survived and three had a fatal outcome.

Symptoms and Physical Findings. Many of the most significant physical findings noted immediately after the onset of subarachnoid hemorrhage have been alluded to in describing the demeanor and general appearance of the patients but there are additional features which should be mentioned. Most patients keep turning from the light and blinking their eyes because of blurred vision and photophobia. Six of the writer's patients had papilledema (elevation of the discs one to two diopters was the average amount of choking), four others had lack of physiologic cupping and indefinite disc margins due to peripapillary edema. Four patients had severe hypertensive retinitis, both recent and old hemorrhages, while four others had fresh retinal hemorrhages associated with marked hyperemia and venous engorgement due to the subarachnoid bleeding.

TABLE 1

Age	No.
Under 20	1
20–30	4
30–40	5
40–50	4
50–60	5
60–72	2
Total:	21

All patients had a stiff neck; many times the rigidity was very marked. Most of them had positive Kernig and Brudzinski signs. There were only two patients in this group who presented evidence of brain damage, localizing in character. A fifty-two year old man with severe hypertensive cardiovascular disease (220/120) had a transitory right hemiplegia. He was found unconscious at home. Two hours later when examined at the hospital he had weakness on the entire right side; but by the following morning there was no longer any evidence of localized brain damage. Nevertheless he expired without ever regaining consciousness due to ever increasing intracranial pressure.

The other patient, a forty-four year old hypertensive (235/140) woman, developed left oculomotor palsy thirteen days after onset as she continued to hemorrhage into the subarachnoid space. Autopsy disclosed massive basal hemorrhage due to rupture of a 1 cm. congenital aneurysm of the left middle cerebral artery at its junction with the circle of Willis. This occurred in 1947 when angiography and operative approach to these problems were not so much in vogue as they are at the present time.[12,13] Of all patients in this series this one would probably have been the best suited to surgical attack.

First of all the aneurysm was large enough so that it could have been shown by x-ray, which often is not the case, and in addition there were localizing signs. Furthermore the risk, however great, would perhaps have been justified because signs of progressive intracranial bleeding foretold a fatal outcome.

The presence of slight fever and leukocytosis was a constant finding and all of the patients had some elevation in spinal fluid pressure. The spinal fluid in every instance was uniformly bloody and became xanthochromic at some time during the period of observation.

Precipitating Factors. It is a generally accepted fact that strenuous physical exertion is not a common causative factor in the production of the initial attack of spontaneous subarachnoid hemorrhage. However, three patients in this series were having sexual intercourse at the time of the attack, one was at stool, one was lifting some boxes in a large department store and one was doing semi-heavy work as a garage repair man. Three were resting or sleeping in bed and the remainder were carrying on the ordinary pursuits of life, except for one feature which appears to have been noted for the first time in this group of patients. The writer does not know of references in the literature to the possible influence of ingested alcohol in connection with the primary attack of subarachnoid hemorrhage. Whether or not consumption of considerable amounts of alcoholic beverages in the immediate to eighteen-hour period before hemorrhage has any bearing on the rupture of an aneurysm may be problematic. The matter was forcibly brought to the attention of the author ten years ago when a seventeen year old girl presented herself for examination with classical signs and symptoms of spontaneous subarachnoid hemorrhage. She gave a history of an alcoholic spree the preceding night and the odor of gin was pungent in her vomitus. The combination of severe basal headache, foggy mentality, visual disturbances, nausea and vomiting plus the alcoholic odor of the vomitus obscured the real diagnosis for several hours and a profound hangover was thought to be the cause of her difficulties. The physical findings were minimal for the first six hours, after which the mental confusion became more apparent, stiffness of the neck appeared, headache became unbearable and finally spinal fluid findings were diagnostic of spontaneous subarachnoid hemorrhage.

In reviewing the history in this series of patients it seems that ingestion of alcohol to the point of inebriation is slightly more in evidence than could be accounted for by mere coincidence. In the immediate to eighteen-hour period before the onset of subarachnoid hemorrhage, five of these patients were admittedly "drunk," eight stated they had been drinking heavily and were "feeling good" or in the throes of a bad hangover at the time of the primary hemorrhage. Of the last group two were drinking wine, three were drinking beer and three were enjoying both beer and whiskey. The author has no explanation for the foregoing observations other than the fact that alcohol is known to exert a powerful vasodilating effect upon the blood vessels in general and upon the cerebral vessels in particular. Could it be then that when thin-walled "berry" aneurysms receive repeated stimuli to dilate they overdo the matter and rupture as a consequence? Six of the patients reported here are, as far as known, "teetotalers" and obviously subarachnoid hemorrhage will occur whether a patient with berry aneurysms has been drinking or not. This matter could be of considerable importance in medicolegal affairs. One of these patients had been drinking beer for many hours when she fell from a stool unconscious, striking her head upon the floor. These facts opened the door to all sorts of speculation but skull x-rays ruled out the possibility of trauma, while spinal fluid findings proved that her coma and subsequent death were due to spontaneous subarachnoid hemorrhage.

Relationship of Other Diseases. Slightly over one-third of these patients had significant hypertension and variable amounts of arteriosclerosis. Four were classified as severe HCVD (blood pressure 210–290/120–150) and four were considered moderate hypertensives (blood pressure 150–180/90–110). While nearly all opinion supports the view that spontaneous subarachnoid hemorrhage may occur regardless of either arteriosclerosis or hypertension,[7] these factors seriously affect the mortality as will be shown later. These patients did not give a history of severe periodic or "migraine" headaches any more than might be encountered in the population at large.

One of the patients had syphilis as manifested by positive serologic studies on both the blood and spinal fluid. His initial attack occurred ten years ago and he remains perfectly well as of this writing. The author believes, as Richardson and

Hyland[4] and others do, that central nervous system syphilis has no etiologic relationship to spontaneous subarachnoid hemorrhage.

The rare causes of subarachnoid hemorrhage, such as liver disorders, purpuras, rheumatic aneurysms, neoplasms and the like, were not encountered in this group of cases.

Mortality. By the end of one year approximately one-half of all patients with spontaneous subarachnoid hemorrhage will have died in either the primary attack or a recurrence[4,8,10] while the remainder will have recovered. The findings of Magee[8] are worth noting in this connection as he observed that 29 per cent of the patients in his series died in the first attack while an additional 21 per cent had succumbed to a recurrence at the end of one year.

The present study, although based on a small number of cases, appears to emphasize more than any other the extremely serious outcome in patients who have hypertensive cardiovascular disease. Of the eleven patients still living, ten have normal blood pressures while only one (thirty-seven years of age) has moderately severe hypertension and her initial attack occurred only a year ago. Of the ten fatalities five had severe HCVD (one of these died of a second attack which came on six months following the first) while three had moderately severe hypertension. A thirty-two year old woman is the only one with normal blood pressure who died during the initial attack from hemorrhage so massive that she never regained consciousness. For the entire group, then, the gross mortality is slightly less than 50 per cent, and in the absence of HCVD there is at the moment an 80 per cent survival in a period of time which extends from one year to ten years and averages about five years. Unquestionably some of these patients will have subsequent attacks as time goes on, particularly the one with hypertension, but this is an unusually high rate of survival even for a five-year average period.

These facts may well cast a little doubt on the current enthusiasm for surgical attack in the majority of these patients. Their condition is so precarious that the danger of so simple a procedure as spinal puncture has been thoroughly heralded. Intra-arterial injection of contrast media followed by craniotomy on patients who are in such perilous state is not without extreme hazard and one wonders whether these things should not be reserved for those who have hypertension or in whom a second seizure follows. Dandy[14] reported two patients alive and well fifteen and twenty-two years, respectively, after the first rupture, while Rosen and Kaufmann[15] told of a patient who died of subarachnoid hemorrhage twenty-seven years after the original attack.

Method of Repair. Details concerning the sequence of pathologic and restorative processes following spontaneous subarachnoid hemorrhage may be found in the excellent publication of Alpers and Forster.[16] They observed that clumping of red blood cells was present from two to six days after rupture and this finding becomes more marked as time goes on. Early the pia-arachnoid begins to plaster itself about the hemorrhagic area and limits the spread of the hemorrhage into the wider subarachnoid space. Connective tissue organization is first in evidence about the third day when reticulum fibers arising almost exclusively from the arachnoid begin to grow into the masses of clumped red blood cells causing them to become segmented. Macrophages then invade, destroy and remove the islets of red blood cells. In the later stages adult collagen fibers finally appear.

TREATMENT

Treatment of spontaneous subarachnoid hemorrhage at the time of the attack should accomplish relief from the excruciating headache, control of the violent agitation and excitement and administration in some manner of proper fluids and nourishment.[1] These matters are fairly obvious and need no further comment but until recently there has been wide divergence of opinion regarding how often and how much to reduce increased intracranial pressure. While most authors admit that removal of spinal fluid may be imperative at times to allay the terrible headache and prevent convulsions, deepening coma and medullary prolapse, it is commonly agreed that the procedure should be carried out with great caution and as infrequently as possible. When, for the reasons stated, the writer has found it necessary to perform therapeutic spinal taps, he uses a twenty-gauge needle and carefully withdraws only enough fluid to bring the manometer reading down to about one-half the original pressure. This routine is similar to the plan of Wolf et al.[11] but they are even more cautious. Some,[1] including the writer, have used hypertonic glucose solution in an effort to reduce intracranial pressure in subarachnoid hemor-

rhage but Ayer[17] is of the opinion that there is no basis for its use and he is no doubt correct.

The period of bed rest is also somewhat controversial inasmuch as Magee[8] facetiously remarks that, "Indeed, as between rest and effort this series suggests that the former deserves the greater share of the blame." However, all patients in the author's series spent a minimum of six weeks in bed and had an additional one- to three-month convalescent period. Caution should be the watchword and allowing ample time for complete organization seems logical to the writer as it does to Sands,[1] Barker[10] and others.

Arteriograms and the surgical management of spontaneous subarachnoid hemorrhage have been discussed at length elsewhere.[10–12,14,18,19]

CONCLUSIONS

1. Spontaneous subarachnoid hemorrhage is a definitive disease entity due specifically to rupture of "berry" aneurysms of the circle of Willis.

2. Rupture is not uniformly precipitated by any known cause such as stresses and strains, but ingestion of large quantities of alcoholic beverages appears to have been a factor in this series of cases.

3. Mortality is greatly increased by associated hypertensive cardiovascular disease.

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Renal Tuberculosis*

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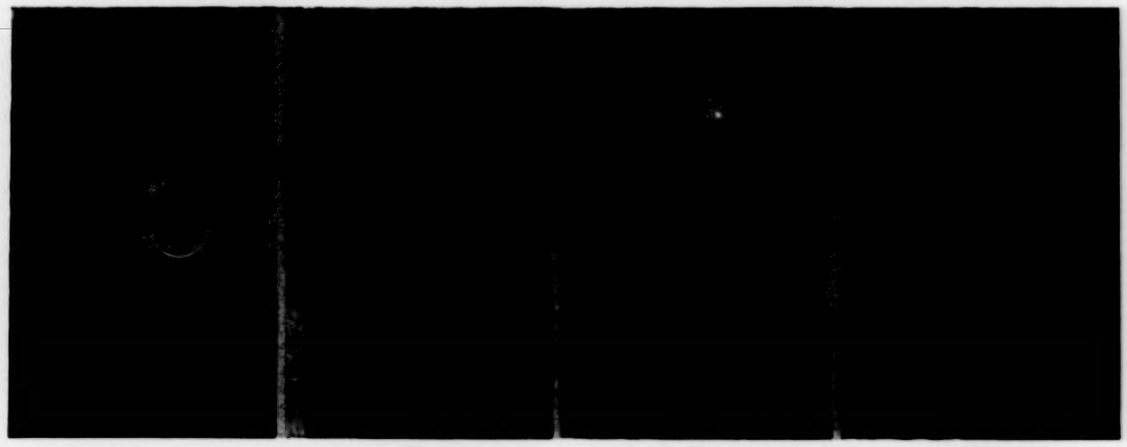
IN some 4 per cent of the patients with pulmonary tuberculosis, destructive tuberculosis of the kidneys develops as a complication of the pulmonary disease. To date we have seen no decline in the incidence of this blood-borne complication as a result of the advent of streptomycin or other drugs.



A B C D

FIG. 1. Progression of renal tuberculosis in a child. Untreated renal tuberculosis is a serious disease which tends to be bilateral. Here it is seen destroying the kidney of a child. A, nine years of age, first visible lesion was a small abscess cavity in the lowest papilla (circle); B, age twelve; C, age sixteen; D, age nineteen (death).

Undiscovered renal tuberculosis can be a very serious complication since it tends to be bilateral. (Fig. 1.) The diagnosis of renal involvement is difficult during the early stages since it is usually asymptomatic for months or years after its onset. By the time urinary burning and frequency appear the disease has usually progressed to an advanced stage for which successful treatment is difficult. The most practical method for searching out early involvement of the kidneys would be routine urine examinations for pyuria in all patients with a history of pulmonary tuberculosis, for a period of five to ten years after their pulmonary infection. The number of pus cells may be as small as 1 to 3 per high power field in urine specimens of specific gravity 1.015, even though the renal lesions are already large.

Pathogenesis. Renal tuberculosis is always secondary to some other focus in the body. In the United States at the present time this focus is usually in the lungs. When hemic dissemination occurs, even though it may involve only small numbers of tubercle bacilli, both kidneys are usually infected. The glomeruli are infected first, causing small "cortical lesions" which often heal spontaneously.[8–10] However, tubercle bacilli which then pass down the convoluted tubule may infect the medulla in the region of the narrow loop of Henle. This more serious "medullary lesion" rapidly grows larger and involves an area in the papilla near the wall of the calyx. This area may become necrotic and slough out, leaving a small papillary abscess cavity which can empty on to the tip of the papilla or in the fornix to either side of the papilla. This small abscess cavity is the first lesion of renal tuberculosis which is detectable by x-ray. (Fig. 2.) As the cavity grows larger it may destroy the entire contents of the renal pyramid above that papilla. The cavity may then extend out to the capsule of the kidney, which tends to sink in

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FIG. 2. Earliest lesion of destructive renal tuberculosis detectable by x-ray is the medullary abscess cavity, representing the contents of a lesion in a papilla which has become necrotic and sloughs out. The center of the papilla seen here (circle) is beginning to slough. The accompanying roentgenogram shows the type of tiny cavity in the tip of a papilla which results (left).

upon the scarred and destroyed pyramid. This indentation can be seen on the surface of kidney especially after the capsule has been stripped back. If the contents of the pyramidal abscess do not slough out, it may be seen as a bulging yellow mass of caseous material under the kidney capsule. These bulges or indentations serve to locate isolated lesions for the surgeon who does partial nephrectomies for tuberculosis.

As the tubercle bacilli and infected caseous material slough into the lumen of the kidney pelvis other calyces are infected directly. The simultaneous hemic infection of several pyramids often occurs, of course.

Stricture formation as a result of the infection and irritation of the infected material escaping into the kidney pelvis, ureter and bladder may choke off the neck of a single calyx, the neck of a major calyx serving half the kidney, or may cause a stricture of the ureter which will destroy the entire kidney with great rapidity. Crippling bladder contractures occurred in 10 per cent of our patients with renal tuberculosis.

The time interval between the primary pulmonary infection and the detection of kidney tuberculosis averaged eight years in one large series with a variation between three and twenty years. The reason for this long delay was the fact that even though destruction was occurring and tubercle bacilli were passing down the ureter, no urinary symptoms were caused for months or years.

Course of the Cavernous Disease if Untreated. The rate of progression of a destructive kidney lesion is unpredictable. Some lesions, even in healthy young patients, can destroy the kidney completely within four years. (Fig. 4.) Other lesions may progress more slowly, taking ten or more years to accomplish total destruction of a kidney. In rare instances the lesions may even heal spontaneously, as by autonephrectomy. The unpredictable nature of the disease makes it necessary to regard every visible renal lesion as a dangerous complication. Since both kidneys are usually infected by tubercle bacilli at the time of any hemic dissemination, both kidneys may later become the site of caseocavernous tuberculosis. It is most common, however, for one kidney to break down first. In approximately 50 per cent of patients the other kidney will begin to break down at some later date if untreated.

Symptoms. Bladder symptoms such as burning and frequency eventually occur after the kidney infection has persisted for a long enough period. Hematuria also eventually occurs in most patients with genitourinary tuberculosis if the infection is permitted to persist. Hematuria occasionally is the presenting symptom since the infection may not yet have irritated the bladder sufficiently to cause urinary discomfort, even though it may have eroded the wall of a tiny capillary somewhere higher in the urinary tract, causing gross bleeding. The hematuria from tuberculosis is usually mild and of short duration. Dull pain over the kidney is frequent. Fever or elevation of the erythrocyte sedimentation rate are rarely found with renal tuberculosis. Pyuria with no pyogenic bacteria on routine urine

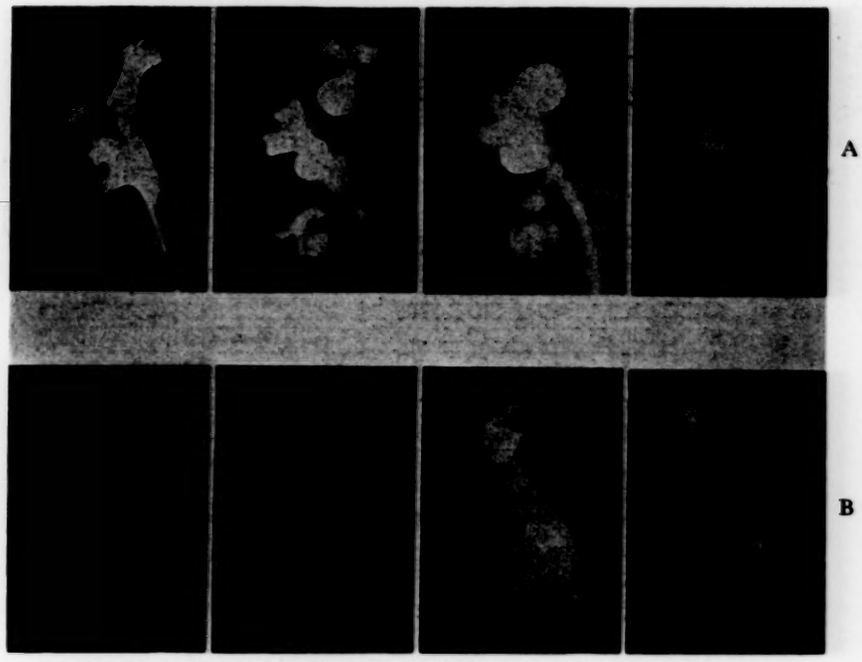

FIG. 3. A, untreated control kidney in a thirty year old man was totally destroyed by tuberculosis in three and a half years (top). B, streptomycin-treated kidney (2 gm. × 120 days) treated at an early stage in a similar patient showed no further destruction (bottom).

culture is a finding which should lead to a suspicion of tuberculosis. Genital infections will eventually occur in the male if the renal lesion is permitted to flourish without therapy. Tubercle bacilli will drop into the prostatic ducts causing caseous destruction which begins in the lumens of the prostatic acini and extends out to destroy areas of the prostatic parenchyma. As this destruction progresses the caseous contents often slough out and the remainder of the prostate contracts. This leaves the prostate gland as a shrunken, hollow, fibrous shell containing tuberculous granulations. Palpation through the rectal wall usually reveals a small prostate gland rather than a large, hard, lumpy gland. As a consequence of the destruction of the secreting parenchyma of the prostate the volume of the semen drops off sharply. Fifty-five per cent of our patients had semen volumes of less than ½ cc. Hard fibrocaseous nodules could be felt on the surface of the prostate in only 25 per cent of our cases. These areas sometimes calcified. The disease may smoulder along in the prostate gland for many years. It may even reactivate during the latter years of life. In rare cases it may die out and cause no further trouble. Tubercle bacilli may descend through the lumen of the ductus deferens to infect the epididymis. Tuberculous epididymitis usually starts as a small nodule, without many symptoms, in the tail of the epididymis. The nodule may have a caseous center for some time but may heal, leaving a fibrous nodule in this area. Still other tuberculous infections of the epididymis can enlarge rapidly causing acute swelling of the epididymis which resembles gonorrheal or Bacillus coli epididymitis in its early stages. This large, hard mass may then soften on one side as liquefaction of its contents occurs. Such an abscess often burrows through the skin and ruptures, causing a spontaneous draining sinus which will last for six to twelve months if untreated. Any draining sinus in the scrotum should be suspected of being tuberculous.

CHEMOTHERAPY FOR KIDNEY TUBERCULOSIS

Streptomycin. The advent of chemotherapy has been a great blessing for patients with this disease. Streptomycin alone, when introduced in 1946, brought about dramatic improvement of symptoms in patients whose bladders were not already contracted. Men with cystitis so severe that they were voiding 120 times in twenty-four hours were relieved within three weeks. This was true whether the urine remained positive for

acid-fast bacilli or not. Many have since resumed useful occupations.

Our five-year follow-up studies after therapy with streptomycin alone (2 gm. daily for 120 days) demonstrated that small lesions (Fig. 3) which had not yet destroyed kidney parenchyma (reduction) in the anticipated number of deaths from uremia has been impressive.

Streptomycin Plus PAS. Combined therapy with PAS and streptomycin given concurrently for a period of one year has given considerably better preliminary results than did streptomycin

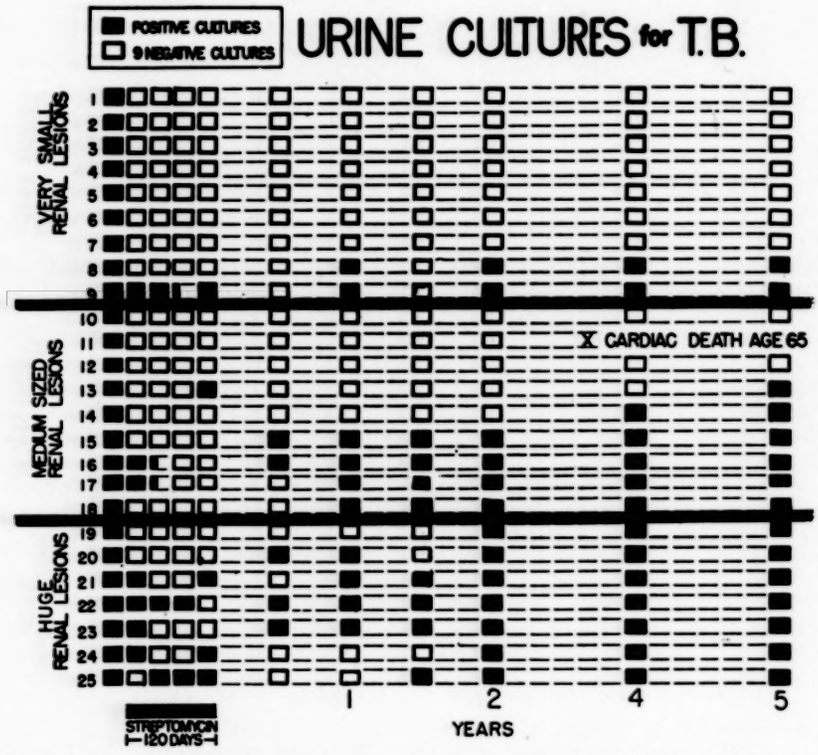

FIG. 4. Five-year follow-up after streptomycin therapy, 2 gm. daily for 120 days. Small lesions, not visible by x-ray (top), showed 80 per cent five-year conversions. Patient No. 13 went five years before relapsing.

to the extent of causing visible cavities by x-ray, were successfully converted to lesions yielding urine negative for acid-fast bacilli in 80 per cent of the cases. Patients who had a single (medium-sized) cavity, involving only one calyx but visible by x-ray, had 20 per cent five-year conversions. Patients who had multiple (large) caseo-cavernous lesions could not be permanently converted by streptomycin alone; there were no five-year conversions in this group. (Fig. 4.) However, some of these patients, after therapy with streptomycin alone, remained negative for periods up to five years before relapsing. Survival rates among these patients have been distinctly better than in the days before chemotherapy. Of one group comprising 458 of our patients, only three have died of uremia. Seventeen others have died of pulmonary disease or miliary-meningeal involvement but the improvement alone. Three groups of our patients were chosen for a comparison of results. All three groups contained equal proportions of large- and middle-sized renal lesions, and each group was of approximately the same size. Figure 5 shows that streptomycin alone gave 37 per cent two-year conversions among these difficult cases. Streptomycin administered daily in doses of 1 gm. in a single injection plus 12 gm. of PAS daily gave 80 per cent immediate conversions of the urine. Streptomycin given twice weekly in doses of 1 gm., plus 12 gm. of PAS daily, gave 90 per cent immediate conversions of the urine to negative. When these groups of patients were followed up two years later, the good results obtained by the combined therapy continued to hold up; (80 per cent two-year conversions in both groups). It appeared from these figures, therefore, that streptomycin plus PAS, given

together for one year, was a more effective therapeutic regimen in converting the urine than was streptomycin alone. It did not appear to matter whether the streptomycin was given daily or twice weekly.

Isoniazid. When isoniazid was given alone, in doses of 300 mg. daily, to a small group of patients whose organisms were already resistant to streptomycin and PAS, approximately 50 per cent converted to lesions yielding negative urines after one year of treatment. These conversions are of such short duration (fifteen months) and the numbers involved are so small that this figure is offered only as a preliminary observation. Another small group who received isoniazid for one year, and whose organisms were sensitive to all drugs, has remained negative to date (one year). At the present time a larger group of patients is completing one year of continuous combined treatment with three drugs, namely isoniazid (100 mg. q.8 h.), sodium PAS (4 gm. q.8 h.) and streptomycin (1 gm. twice weekly).

Isoniazid alone appears to have the same drawbacks as streptomycin in that it does not convert large caseous renal lesions readily, and drug resistance may occur after several weeks of treatment. Leukopenia has been reported from isoniazid in a few instances (we had one case of thirty). In addition, this drug has a distinct danger for patients who are uremic. It has been our experience that patients who have an elevated blood urea nitrogen may accumulate isoniazid in the blood if full doses are given. Isoniazid is a central nervous system stimulant and, in addition to causing hyper-reflexia, sphincter spasm, nervousness, etc., may cause convulsions if the blood level rises too high. For this reason we have determined blood levels in all patients who showed any elevation of blood urea nitrogen or whose kidney function was diminished. We found it inadvisable to give the usual doses of 300 mg. daily to patients whose blood urea nitrogen levels were elevated since their blood levels of isoniazid rose to 8 mg. per cent, two or three times higher than the usual blood level. It is our practice therefore to reduce dosage levels to 200 mg. daily in patients who are uremic. If the patient feels too irritable we reduce the dose further. It was thought advisable to obtain isoniazid blood levels, if possible, in uremic patients throughout their treatment. There has been no sign of nephrotoxicity; for example, the BUN of one of our patients, which was 200 mg. per cent before treatment, came down to 30 mg. per cent during isoniazid treatment. This precipitous drop was primarily due to re-establishment of electrolyte balance.

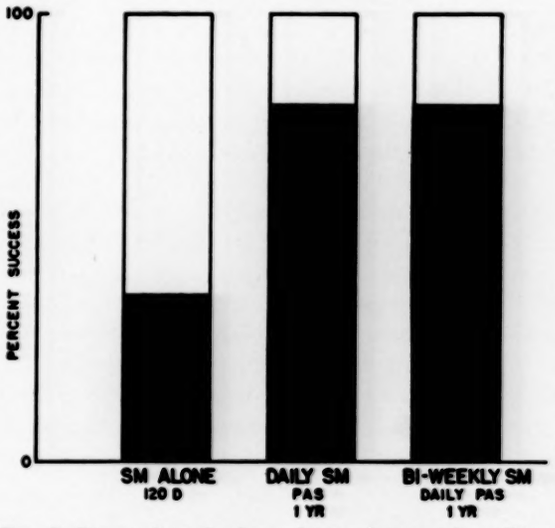

FIG. 5. Conversion of urine cultures; large and medium renal lesions; twenty-four-month follow-up. Streptomycin twice weekly, plus PAS daily (right hand column), was just as effective in converting the urine to negative as streptomycin daily, plus PAS (middle column). Both were better than streptomycin alone (left hand column).

PROSTATIC TUBERCULOSIS

Prostatic lesions which have resulted from and coexist with renal lesions, or which remain after a tuberculous kidney has been removed are currently being treated with the combined regimen of streptomycin, PAS and isoniazid (as already outlined) for a period of at least one year. The results to date with prostatic lesions are just as good as with renal lesions. It is hoped that chemotherapy will be more satisfactory than radical prostatovesiculectomy, which is fraught with technical dangers. We advise this operation only in cases with intractable pain. Such cases fortunately are rare.

EPIDIDYMAL TUBERCULOSIS

The patient's fertility status is considered in making decisions as to whether or not to remove a tuberculous epididymis. If the patient is sterile we may proceed with epididymectomy after at least three weeks of chemotherapy. Chemotherapy is then continued for a period of one year on the premise that there is probably active disease in the prostate as well as in the epididymis.

If the epididymitis is unilateral and the sperm count is normal, we remove the infected epididymis. If both epididymides are infected but the patient is very desirous of risking everything for the possibility of having children, we do not remove the epididymides but do continue with chemotherapy in the hope that the ductus deferens will recanalize around the tuberculous abscess. This has happened in two of our patients who now have normal sperm counts. One of these patients has recently had his first child. We do not tie off the vas if the patient wants children. We have had no new cases of epididymitis which developed after one year of chemotherapy. However, some tuberculous abscesses of the epididymis did grow larger during therapy.

Urine cultures for Mycobacterium tuberculosis taken during chemotherapy are likely to show no growth and lead to a false assumption that the disease had been arrested. Data based on 398 specimens (1,194 cultures) from six of our patients receiving isoniazid for one year indicated that it was safer to wait ten days after the cessation of one year of treatment before collecting urine specimens for culture. In that way treatment will not be prematurely interrupted because of false-negative cultures.

SUMMARY

All patients who have had pulmonary, osseous or other tuberculosis should have periodic urinalyses for pyuria. The search should be kept up for ten years after the pulmonary infection. Even small numbers of pus cells (one to three per HPF) should lead to an investigation for renal tuberculosis. Multiple guinea pig inoculation and cultures of the urine for tubercle bacilli should be carried out.

Unilateral, destructive tuberculosis of the kidney is probably best treated by nephrectomy, in conjunction with one year of combined treatment with streptomycin and PAS. To date the presence of any lesion large enough to be visible by x-ray has heralded a poor prognosis for permanent conversion by chemotherapy alone. It is possible that longer observation of the newer chemotherapeutic regimens, especially those employing isoniazid in combination with streptomycin and PAS, may justify a trial of at least one year of chemotherapy before surgery is advised. There is certainly no emergency about performing a nephrectomy for tuberculosis. It is desirable to postpone the operation long enough to make certain that the urine from the contralateral kidney is free of tubercle bacilli and pus cells. The operation is best preceded by four months of chemotherapy and followed by eight more months of treatment.

In selected cases in which the disease has not yet spread beyond one portion of the kidney but the destruction of that portion is so extensive as to indicate a poor prognosis through chemotherapy alone, partial resection of the involved area of kidney may be advisable. It has been our policy to precede this operation with from four to six months of combined therapy with streptomycin and PAS and to continue the therapy after operation until at least one year of continuous treatment has been given.

Bilateral, inoperable renal tuberculosis is now treated with combined chemotherapy for a period of at least one year. If the pyuria persists after one year of treatment, a second year of treatment may be given. Patients are kept on a semi-ambulatory rest regimen employing isoniazid, streptomycin and PAS together for a period of one year. Some patients are being observed for a second year. If one kidney is worse than the other, the worse kidney should not be removed in the hope that the disease will abate; the patient will only die sooner.

Prostatic and epididymal tuberculosis are now being treated with one year of combined chemotherapy. Epididymectomy is advised only for lesions which are obviously very large, caseous or necrotic or in which the ductus deferens is already occluded. The operation is followed by one year of combined chemotherapy.

Five years of observation of bacteriologic data, roentgenographic data, symptomatic and survival data have convinced us that modern chemotherapy is certainly effective in modifying the formerly lethal course of renal tuberculosis. A careful search for small numbers of pus cells in the urine of all patients with a history of pulmonary tuberculosis is the most valuable test for early detection and successful treatment.

Acknowledgment: We wish to express our appreciation for the unfailing assistance of our bacteriologists, Dr. Michael Kenney and Mr. Milton Goldman, head nurse Lydia R. Sechler and her staff, our secretaries Miss Alfreda Jastremski and Miss Diana Wild, illustrators Lubin, Kantor and Hession and the Departments of Roentgenology and Urology of the Kingsbridge Veterans Hospital, Bronx, New York.

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Seminars on Antihypertensive Drugs

Management of Arterial Hypertension*

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CHRONIC arterial hypertension is believed to cause increased cardiac work leading to myocardial hypertrophy and, in some cases, to dilatation and failure of the heart, and to arteriolar nephrosclerosis resulting sometimes in renal insufficiency. In addition, the rate of progression of atherosclerosis is thought to be increased, leading especially to occlusive disease of the coronary and cerebral arteries or to rupture of the latter. In certain instances, especially when combined with primary renal disease, the condition becomes "malignant," often resulting in early death. If the blood pressure were controlled at normal levels, some or all of these effects of chronic hypertension might be prevented or delayed while others might be enhanced.

For a regimen to be effective against arterial hypertension all patients should respond favorably, the response should be unequivocal, normotension sustained for long periods should be common, the responses should be so obvious that no other explanation for them is tenable and the progress of the serious secondary effects of hypertension should be halted, delayed, postponed or reversed. Furthermore, the regimen should not be harmful or hazardous to the patient, new diseases or other serious conditions should not be produced and gradual reversal of the primary process should result. Proof of the effectiveness of any antihypertensive regimen depends not only upon achieving sustained lowering of blood pressure but also principally upon preventing the serious and fatal secondary effects of hypertension. In the present study the aim of treatment was sustained normotension.

There are enough potent antihypertensive substances now available to lower the elevated blood pressure in all cases of arterial hypertension effectively; sustained control at lower levels is possible in all but rare cases. The questions facing the physician are no longer: "Can hypertension be treated"? or "Should hypertension be treated"?, but are now: "How should it be controlled, to what extent, and what are the hazards of control"? Prevention or retardation of the serious consequences of the condition is therefore possible and practical for the short term, unless (1) pathologic damage to the kidney has advanced to the point of causing uremia or severe renal insufficiency, (2) atherosclerosis of vital arteries has progressed to the point of initiating thrombosis or (3) the drugs used cause late toxic reactions. Data which corroborate these statements based on experiences with new therapeutic methods during the past thirty-four months in over 300 patients are reported here. Only drugs now available and effective orally will be discussed and changes in the most severe stages of hypertension considered.

RATIONALE

Methods of treatment were based upon hypotheses of pathogenesis proposed several years ago[1,2] and considered at length.[3] Briefly, these theories are as follows. Persons predisposed to hypertension react to emotional and other stresses by vasospasm mediated through the sympathetic nervous system; this relative sympathetic overactivity may be the result of hereditary or developmental influences. The kidneys take part in the vasospasm, a functional renal ischemia, releasing humoral vasoconstrictor substances which have a prolonged action. For unknown reasons repeated episodes of transient generalized vasospasm eventually result in permanent vasospasm accompanied by release of humoral pressor substances from the ischemic kidney. Sustained vasospasm causes changes in

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arteriolar walls, especially those of the kidney, producing organic renal ischemia and maintaining the hypertension. Therefore, early hypertension may be predominantly neurogenic, late hypertension may involve both neurogenic and nephrogenic components, and severe hypertension may be predominately nephrogenic with neurogenic components engrafted upon it; the course of any type may be adversely modified by primary disease or dysfunction of the autonomic nervous system, kidneys or adrenals.

If this idea is correct, it is obvious that two simultaneous approaches must be made to control severe stages of hypertension. The neurogenic sympathetic influence must be blocked or abolished and the pressor substances in the blood simultaneously inactivated. Agents or procedures effective against one factor can be expected to cause alterations in the condition only to the extent of the individual contribution of that factor to the total picture. For example, in mild and moderate stages depression of the activity of the sympathetic nervous system by surgery or drugs may cause reversal of the process; in long-standing severe and malignant stages the same alteration may often result in only slight to moderate changes unless the nephrogenic factor is also controlled.

DRUGS AVAILABLE AND THEIR ACTIONS

Four agents now available characterize different actions; each appears to be "specific" in the sense that one of the pathogenic mechanisms of hypertension is directly or indirectly affected.

Acting on Central Nervous System. The whole root of Rauwolfia serpentina has been found to be a mild antihypertensive agent for many years[4] and appears to aid in allaying anxiety. Introduced into this country by Wilkins,[5] it has achieved wide popularity. It contains at least fourteen alkaloids.[6] The action of an active alkaloid, reserpine, is primarily upon cerebral sympathetic centers, probably in the posterior hypothalamus or cortex.[7] It is a derivative of yohimbine. The pure alkaloid is 500 to 1,000 times as potent as the whole root. Toxicity is low. Mental depression, unpleasant dreams, drowsiness and apathy have accompanied its use in a small proportion of subjects; we have not given it to patients upon whose judgment and reactions the lives and welfare of others depend. Many patients have reported a sense of well-being and mental quietude,* a phenomenon impossible to evaluate accurately. Stuffy nose and loose stools are common; epistaxis has been observed. Electroencephalographic patterns are not altered in the monkey.[8] Our experience has been limited to one year.

Acting on Autonomic Ganglia. Hexamethonium chloride blocks the ganglionic transmission of sympathetic and parasympathetic impulses,[9] presumably by competing with some natural quaternary ammonium compounds. The desirable effect is upon the sympathetic ganglia, the undesirable upon the parasympathetic. As a drug it is remarkably non-toxic in the sense that it has no true side effects other than those due to its primary action. It has caused total obstruction of various viscera when partial organic obstruction was present but unrecognized.[10] Excretion is rapid[3] requiring frequent (four-hour) and regular administration for sustained effects. Only about 10 per cent of an oral dose is absorbed; the duration of action is short (four hours).[11]

Oral administration of hexamethonium requires that two precautions be taken: (1) the prevention of obstipation and accumulation of excessive quantities in the gastrointestinal tract and (2) the prevention of hypotension. In the present study the first precaution was taken by the use of daily laxatives and the second by the patient regulating his own dosage according to the prevailing level of blood pressure at four-hour intervals. Unless there has been obstructive disease of hollow organs, we have found hexamethonium chloride a safe drug to use continuously for many months in over 300 patients. In malignant hypertension fatal interstitial pneumonia may appear, especially in Negro patients with poorly controlled hypertension.[10,12] Our experience with this agent is limited to thirty-five months.

Hexamethonium salts given orally alone did not have the beneficial effects so widely claimed; about half our patients in severe stages responded little or not at all to full therapeutic doses, and in the remainder a sustained hypertension was at best converted into a fluctuating one. Ganglionic blockade induces postural falls in blood pressure.

A minor but definite improvement appears to lie in the ganglionic blocking agent, pentapyrrolidinium bitartrate, given extensive use by

* Strangely enough, some individuals have complained of increased anxiety, nervousness, tension and insomnia while taking this drug.

Smirk[13] and introduced into this country by Freis et al.[14] The duration of action is longer (up to six hours)[13] and less constipation and hypotonicity of the bladder are induced than with methonium salts. Possibly because comparably larger oral doses can be tolerated, this blocking agent is often more effective than hexamethonium chloride. Our experience with it is limited to six months.

Acting on Parasympathetic Nervous System. Protoveratrine, a mixture of two alkaloids from Veratrum alba, acts upon the parasympathetic nervous system in some manner not thoroughly understood, possibly upon the higher centers,[15] the carotid sinus or vagus.* The net result is stimulation. Therefore, the neurogenic factor is only indirectly affected. The drug also acts upon the vomiting center in doses close to therapeutic ones. Hypotensive action is not prolonged. Our experience is limited to one year using the pure alkaloids and six years using the whole plant preparation. Protoveratrine was found to produce a fluctuating hypotension, lower levels being maintained for several hours and then "escape" occurring in spite of repeated doses. In mild and moderate stages some benefit was occasionally noted but the difficulty with the dosage schedule and with vomiting usually caused a change to more tolerable agents.

In general, these three agents have been found to affect neurogenic hypertension of mild to moderate degree favorably. Reserpine has caused sustained normotension in mild stages of the disease in about half the subjects; it is a definite antihypertensive agent of mild potency.[5] Ganglionic blocking agents have caused fluctuations in blood pressure and postural hypotension; falsely favorable results can be obtained if the blood pressure is measured with the patient standing (as is the case for a variable interval following surgical sympathectomy).

Acting on Vascular Smooth Muscle or Kidney. The nephrogenic factor is apparently controlled by some substituted hydrazines, notably 1-hydrazinophthalazine. Pherentasin is directly inactivated by this agent and the pressor action of some but not all primary amines inhibited in a manner not understood.[16] This drug affects the neurogenic factor little if at all, except in very large doses. The evidence that this agent acts upon smooth muscle of blood vessels is obscure and indirect.[17] Central nervous action is possible but has not been proven.[18] Large doses are required to inhibit the action of nor-epinephrine, while in the rat that of serotonin is enhanced.[16] Renal vasodilatation in the face of a lowered blood pressure occurs,[18,19] making it a unique drug.* The known actions of the hydrazines include binding of certain heavy trace metals, combination with sulfhydryl compounds and attachment to carbonyl groups.[16,20] Amino acid decarboxylase is inhibited *in vitro*.[21] † The drug is excreted rapidly, requiring frequent and regular administration at four-hour intervals.

Control is achieved at the expense of the antihistaminase activity of the drug (and many of its analogues).[22] Failure of destruction of liberated histamine probably leads to headache, generalized but slight edema, production of the diencephalic blush and associated symptoms, and possibly nausea. Fortunately these phenomena usually last only a few days, are not present in a majority of individuals, produce little and temporary disability, and are not severe enough to cause withdrawal. They are less severe when hexamethonium ion has been given previously.

1-Hydrazinophthalazine alone is only moderately effective. We have not seen sustained normotension produced in more than a very few individuals.[23] Best results are achieved in patients in the malignant stage, after unsuccessful sympathectomy and with mild benign hypertension but the changes, while significant, are seldom dramatic. Collagen disease results from prolonged administration in about 10 per cent of patients.[10,24,25] Our experience covers nearly five years.

* The carotid sinus may be blocked through stimulation of a central reflex arc via the vagus. There is no evidence, however, that the emetic and hypotensive actions of the drug can be dissociated by purification of the alkaloids or by recourse to chemical relatives.

* In man the available evidence suggests that substituted hydrazines act peripherally on some unknown but very fundamental mechanism concerned with vasoconstriction which is not mediated through autonomic nerves. In animals a direct action on vascular smooth muscle apparently occurs; the drugs produce dilatation in the constricted vessels of the isolated limb, the coronary arteries, the intact mesenteric, femoral and renal vascular beds, the whole nephrectomized animal and the vasoconstricted spinal cat.[18] This interesting substance appears to lower peripheral resistance throughout the vascular bed and to be more effective on constricted than on dilated vessels. Whether the effect is on the "nephrogenic" factor or not awaits elucidation of its fundamental chemical reactions.

† Possibly by combination with carbonyl groups or a metallic coenzyme.

Other Agents. Many other available and experimental drugs were tested. None exhibited potencies comparable to those mentioned. Of the sympatholytic agents available, dihydrogenated ergot alkaloids, regitine® and dibenzyline® were given to a total of ten patients in severe stages in lieu of hexamethonium ion; results were poor. Several experimental ganglionic blocking agents were substituted in eight; effects were less than with hexamethonium chloride. These experiments will therefore not be detailed.

DEFINITIONS AND ANALYSIS OF DATA

Essential to therapy and to accurate evaluation thereof is not only a knowledge of the pharmacologic actions of the drugs but especially an estimate of the stage of the hypertensive process present at the time treatment is begun. Since these new agents combat vasospasm and only indirectly affect the pathologic changes caused by chronic arterial hypertension, the degree and constancy of the vasospasm must be estimated without undue consideration of pathology other than renal insufficiency. For example, the rate of development of atherosclerosis may be hastened by hypertension but secondary changes due to the presence of this other disease are not directly attributable to the condition being treated. Coronary occlusion or cerebral vascular accident can occur as a result of atherosclerosis in the presence of mild, moderate or severe hypertension or normotension. Since only hypertension was being treated, its severity and lability were estimated in each case by commonly used clinical methods, disregarding atherosclerotic complications (coronary occlusion, cerebral vascular accident, cerebral atherosclerosis) which of necessity must be considered in every case requiring surgery.

As a beginning, the stage of the hypertensive process alone was graded, disregarding secondary conditions due to atherosclerosis and congestive heart failure, by the following: the status of the ocular fundi, the level of arterial pressure and especially its variability from hour to hour and the degree of depression of renal function when primary renal disease was absent. The stages are more or less conventional:

Normotensive. Systolic always below 140 mm., diastolic below 90 mm.

O. Prehypertensive. Systolic usually 140 mm. or below, diastolic usually 90 mm. or below except under stress (no cases).

I. Mild Benign. Normal at complete rest, systolic 150 to 180 mm. most of the time, diastolic 90 to 105 mm. most of the time; blood pressure falls to normal during hospital admission (cases discussed in general terms only).

II. Moderate Benign Hypertension. Blood pressure always elevated at rest in bed but falls to normal levels during heavy sedation with sodium amytal; ocular fundi, grade I or II (Keith-Wagener); renal function as measured by the fifteen-minute excretion of phenol red (P.S.P.) normal or nearly normal (25 per cent or greater); diastolic pressure usually 105 to 120 mm. Hg, systolic 180 to 220 mm. during rest in bed, remaining elevated at night; congestive heart failure and apoplexy may have occurred (twenty-six cases).

III. Severe Benign Hypertension. Blood pressure not falling to normal during sleep induced by sodium amytal; ocular fundi; grade I or II; renal function normal or depressed without retention of nitrogen in blood; diastolic pressure usually 120 to 160 mm. Hg, systolic 200 to 270 mm. during rest in bed; severe secondary pathologic complications present or absent (172 cases).

IVa. Early Malignant Hypertension. Diastolic pressure always 130 to 160 mm., systolic 200 to 280 mm.; renal function reduced but without retention of nitrogen in blood; ocular fundi, grade III–IV; albuminuria and abnormal microscopic elements present (twenty-four cases).*

IVb. Severe Malignant Hypertension. Diastolic pressure always 130 to 200 mm. Hg, systolic 200 to 300 mm.; borderline renal function or slight elevation of non-protein nitrogen in blood (up to 30 mg. per cent; upper limit of normal by Somogyi zinc method, 25 mg.); ocular fundi, grade IV (thirty-one cases).

IVc. Decompensated Malignant Hypertension. Nitrogen retention present; systolic pressure 200 to 300 mm. Hg, diastolic 130 to 220 unless congestive heart failure is present; ocular fundi, grade IV (forty-one cases).

* We have presumed for therapeutic purposes to include this group as representing a clinical approximation of the early or transition stage of the "malignant" phase, since many cases will show rapid progression. The difference lies in the absence of one of the three findings of grade IV ocular fundi: hemorrhage, exudate or papilledema. Actually papilledema was present in ten patients, blurred optic discs in eight and retinitis with clear discs in six. We fully realize that these signs sometimes disappear spontaneously. The clinical state, "malignant hypertension," is not to be confused with the pathologic condition, "malignant sclerosis," with arteriolar necrosis, seen in patients dying with renal insufficiency.

Uremia. Non-protein nitrogen more than 100 mg. per 100 ml. plasma; uremic symptoms present (ten cases).

The condition of each patient was re-estimated at one- to three-month intervals of therapy. The latest period reported herein varied from thirteen to thirty-four months after discharge from the hospital but in each case represented the most recent findings. The criteria were similar except for those involving the range of blood pressure, which were made more rigid. Because of hourly fluctuations we have preferred to grade each therapeutic result as follows:

Therapeutic Grade 0: Blood pressure always normal.

Grade 1: Blood pressure normal 80 per cent of time or more, systolic never over 160 mm., diastolic never over 100 mm.; elevation only with emotional tension; average level normal.

Grade 2: "Reasonable" levels of blood pressure; systolic 160 mm. or below 80 per cent of time, never over 180 mm., diastolic 95 mm. or below 80 per cent of time, never over 110 mm., frequent fluctuations to normal levels; average levels 150 and 90 mm.

Grade 3: Moderately hypertensive levels of blood pressure; systolic 180 or below 80 per cent of time, never over 200 mm., diastolic 100 mm. or below 80 per cent of time, never over 120 mm.; occasional fluctuation to normal levels.

Grade 4: Consistently hypertensive levels of blood pressure; systolic 200 or below 80 per cent of time, diastolic 120 or below 80 per cent of time; no fluctuations to normal levels.

In patients in whom therapeutic Grade 3 was obtained with full therapeutic doses of both drugs, the result was considered resistant. When smaller doses were given in order deliberately to achieve a Grade of 3, the result was considered elective. All levels of blood pressure considered were those measured by competent nurses in the hospital or by patients or members of their families at home, checked by a physician from time to time. Levels obtained before or on admission to hospital by house officers or physicians were disregarded in estimating stages of the disease.

METHOD FOR SEVERE AND MALIGNANT STAGES (HYPHEX)*

The method has been published in detail.[3,26] In brief, the treatment is commenced in the hospital. Blood pressure is measured in the supine position every four hours, day and night, by competent nurses. After several days' interval for clinical and laboratory examinations, the oral administration of hexamethonium chloride is begun in small doses, usually 125 mg., every four hours, increasing by daily increments until 500 mg. per dose is reached. At that point one-half, three-quarters or all of the dose is omitted if the systolic pressure is below 140, 130 or 120 mm. Hg, respectively (slightly higher "omit" levels are used in elderly individuals, those with atherosclerosis of coronary or cerebral arteries and patients with renal insufficiency). 1-Hydrazinophthalazine is then given additionally in small doses at four-hour intervals, increasing daily until 100 mg. per dose is reached. This agent is continued regardless of the level of blood pressure, except under extraordinary circumstances. If the blood pressure is uncontrolled or only partly controlled, the dose of one drug at a time is increased daily until results are obtained; seldom has it been necessary to give more than 750 mg. per dose of hexamethonium chloride or 150 mg. per dose of 1-hydrazinophthalazine. Reactions and side actions are treated as they occur; those due to 1-hydrazinophthalazine by antihistaminic agents, autonomic paralysis by urecholine and daily laxatives and those caused by a fall in blood pressure by rest in bed and waiting until readjustment takes place. It is essential that the bowels move daily and that laxatives be used regularly in order to prevent obstipation (usually milk of magnesia and cascara, followed by magnesium citrate if constipated).

After optimum control is achieved the dose at 2 or 4 A.M. is omitted to insure eight hours' rest; the usual result is a rise in the "resting" blood pressure upon awakening caused probably by elimination of both agents during the night. Blood pressure is then recorded in the sitting position in order to prevent severe hypotension while standing, the dose of hexamethonium chloride being "automatically" adjusted accordingly. Patients are taught to measure their own blood pressure in the sitting position and are discharged from the hospital with instructions to continue the schedule, omitting part or

* The word "hyphex" is used to describe the method of administering the two drugs hexamethonium chloride and 1-hydrazinophthalazine (hydralazine, apresoline®) by the oral route in doses sufficient to lower elevated blood pressure, with variation of the dosage of the former according to the prevailing level of blood pressure.

all of the hexamethonium chloride if the systolic pressure before each dose is below 140, 130 or 120 mm. Hg, and to regulate the bowels with suitable laxatives. By such precautions hypotensive episodes and obstipation can be avoided. A chart is maintained of each recording of blood pressure (five a day), providing adequate data of about 150 measurements a month and 1,800 a year. Education of the patient is an essential requisite to proper control. After six to twelve months of normotension or near normotension one dose of each drug may be omitted and later another, if the blood pressure remains lower. In some patients with severe secondary complications or unsuccessful sympathectomy, elective partial control instead of full control is employed to avoid hypotensive episodes. Acute hypertensive emergencies were treated by parenteral administration of the drugs according to published methods.[3,26]

If the blood pressure was not adequately controlled after a year or more (therapeutic Grade 3) additional drugs were added to the program, especially reserpine, given in 1.0 mg. doses at bedtime daily. The effect was evaluated not only upon the levels of average pressure but also upon the mean weekly dose of hexamethonium chloride, providing a "double-check" upon the effectiveness of the new agent.

CLINICAL MATERIAL FOR HYPHEX METHOD

Hyphex, the combination of hexamethonium chloride and 1-hydrazinophthalazine, was used in all patients considered to be in Stages III and IV inasmuch as no other procedure was found to give comparable results. A small number in Stage II were also subjected to this regimen. No other measures such as diet, sedation, surgery or psychotherapy were employed. In order to subject the method to as severe a test as possible no patient was refused treatment because of the severity of hypertension or of its complications. Cases were selected in that patients whose average blood pressures fell with rest in bed to 180 mm. systolic or below, and 120 or below diastolic were not treated unless congestive heart failure or cerebral vascular accident was present. Of the first 100, all suffered from severe chronic or malignant hypertension and its secondary effects; of the remainder, requirements were broadened to include a few in moderate benign stages and others with severe hypertension and less serious or beginning complications. Persistent chronic hypertension had been well documented in every case. Forty-one had suffered one or more cerebral vascular accidents, thirty-five a previous coronary occlusion; thirty-seven were in various stages of congestive heart failure; ninety-six were in malignant stages of hypertension and ten were in terminal uremic states secondary to primary renal disease or nephrosclerosis; renal insufficiency was present in forty-one; twelve exhibited signs of severe cerebral atherosclerosis and fourteen were severely ill with acute cerebral edema. There were 137 white and eight Negro males; 140 white and nineteen Negro females. Their ages ranged from six to eighty, but there were only two children and four patients older than seventy; most were in the fifth to seventh decades of life. Sixty-two were ward patients and 242 were private patients. Ten to fifteen patients per month were added to the series and 150 were begun on treatment between August, 1951, and August, 1952. Of those in malignant stages, thirty have been treated for twenty-four to thirty-four months and twenty-one for fourteen to twenty-four months; in less severe stages, 121 have been treated for eighteen to thirty-four months. For purposes of analysis this series was closed on May 1, 1953.

METHOD FOR MILD AND MODERATE STAGES

Because the precautions essential for continuous effective use of hexamethonium chloride are cumbersome but unavoidable in severe stages of hypertension (repeated measurements of blood pressure and gradation of dose), patients in less severe stages were treated with 1-hydrazinophthalazine alone or in combination with reserpine. When normotension was not established, it was necessary to resort to hyphex; otherwise blood pressure was measured only occasionally by physicians, to the detriment of the data. The usual method was to give 1.0 mg. of reserpine daily at bedtime with increasing doses of 1-hydrazinophthalazine until relative normotension occurred and was sustained. When examination in the hospital was accompanied by a fall of blood pressure to relatively normal levels, reserpine alone was used. When the blood pressure fell only during sleep induced by sodium amytal, the two agents were given together. Attempts to avoid the use of hexamethonium chloride were made but were unsuccessful in severe stages; about two-thirds of patients in moderate stages were able to achieve normotension without this agent. Definitive discussion

of the results is therefore impossible with inadequate data.

RESULTS OF HYPHEX IN MALIGNANT HYPERTENSION

Mortality. The mortality due to hypertension and to other causes in adequately treated patients is shown in Tables I and II. The survivals compare favorably with a control group considered to be suffering from conditions of similar severity; the difference between the two groups lies only in that patients in the second failed to cooperate by continuously taking both drugs or that their physicians discontinued one or both for various reasons. Return of hypertension was consistent in all. Every patient but three died within a month of discontinuation of both drugs and in one to eighteen months of discontinuation of only one. Patients surviving three months and

TABLE I

GROSS MORTALITY OF PATIENTS TREATED WITH HYPHEX FOR THIRTEEN TO THIRTY-FOUR MONTHS

Stage of Hypertensive Disease	Adequately Treated				Discontinued Treatment*				Discontinued (%)
	Cases (No.)	Living	Dead	Mortality (%)	Cases (No.)	Living	Dead	Mortality (%)	
Uremia	10	...	10	*100*	..	..	..	....	..
IVc: Nitrogen retention									
NPN > 60 mg. %	2	1	1	(*50*)	4	..	4	*100*	*34*
NPN 30–60 mg. %	25	19	6	*24*	10	..	10	*100*	
IVb: Adequate renal function	23	18	5	*27*	8	..	8	*100*	*26*
IVa: Early malignant stage	18	16	2	*13*	6	3	3	(*50*)	*25*
Total excluding uremia	68	54	14	*21*	28	3	25	*89*	*29*
III: Severe "benign" hypertension	144	139	5	*3.6*	28	19	9	*32*	*16*
II: Moderate "benign" hypertension	18	18	0	*0*	8	5	3	(*38*)	*31*

Duration of Treatment

Time (mo.)	Adequately Treated				Discontinued Treatment†			
	Stage IV		Stage III		Stage IV		Stage III	
	Living	Dead	Living	Dead	Living	Dead‡	Living	Dead§
24–34	30	..	64	1	1	.....	..	1
18–24	15	..	52	1	..	3(2)	1	3
13–18	9	4	23	2	..	(2)	5	..
6–13	..	..	..	..	1	(1)	3	..
3–6	..	5	..	..	..	8(6)	4	1
1–3	..	5	..	1	..	(4)	1	1
<1	..	..	..	..	1	(7)	5	3

* Hexamethonium chloride discontinued in three, both agents in twenty-five of Stage IV. In Stage III hydralazine was discontinued in thirteen (four deaths) and both agents in fifteen.

† One or both drugs discontinued after period shown.

‡ Numbers in parentheses indicate patients who died four to thirty days after discontinuing treatment. Others died within thirty to sixty days. All deaths were from hypertensive complications.

§ Deaths occurred within one to six months after discontinuing treatment.

not dying of interstitial pneumonia exceeded the survival time of two-thirds of individuals reported by Schottstaedt and Sokolow,[27] i.e., nine months. The three survivors who stopped therapy showed early signs of the malignant stage which disappeared; at present one is only moderately hypertensive and two severely so.

slightly hypertensive (Grade 1) and seven are normotensive (Grade 0). Renal function has slowly improved in all but two cases and non-protein nitrogen in the blood decreased in ten of those with renal insufficiency. The therapeutic grades of blood pressure are shown in Figure 1. An example of the extremes of blood

TABLE II

CAUSES OF DEATH IN ALL STAGES*

Complications	Continuing Treatment (230 Cases)						Discontinuing Treatment (64 Cases)					
	IVc	IVb	IVa	III	II	Total	IVc	IVb	IVa	III	II	Total
Hypertensive												
Uremia	..	..	..	....	..	..	4(2)†	..	..	....	..	4
Uremia developing	2	..	..	....	..	2	3	4	..	....		7
Cardiac failure	..	..	..	....	..	1	1	1	..	2	1	5
Cerebral hemorrhage	1‡	..	..	1§	..	2	1	1	1	2	1	6
Cerebral arterial thrombosis	..	1	..	1	..	2	.....	..	1†	....	..	1
Cerebral edema	..	..	..	....	..	..	1	..	..	....	..	1
Coronary occlusion	..	..	..	3**	..	2	1	..	..	1††	1	3
Dissecting aortic aneurysm	..	..	..	....	..	..	..	..	..	1††	..	1
Sudden death while hypertensive	..	..	..	....	..	..	1	..	..	1	..	2
Unknown while hypertensive	..	..	..	....	..	..	2	2	1	2	..	7
Subtotal	3	1	0	5	0	9	14	8	3	9	3	37
Non-hypertensive												
Acute interstitial pneumonia‡‡	2	1	1	....	..	..	.....	..	..	....	..	..
Bronchopneumonia	1	1	..	....	..	..	.....	..	..	....	..	..
Post-operative shock	..	1	..	....	..	..	.....	..	..	....	..	..
Carcinoma of lung	..	..	1	....	..	..	.....	..	..	....	..	..
Carcinoma of gallbladder	..	..	..	....	..	..	.....	..	..	1	..	1
Died in sleep—unknown while normotensive	2	1	..	....	..	..	.....	..	..	1††	..	1
Subtotal	5	4	2	0	0	11	0	0	0	2	0	2
Total	8	5	2	5	0	20	14	8	3	11	3	39

* Excluding ten uremic deaths occurring during first hospital admission.
† Discontinued hexamethonium chloride only.
‡ Three cerebral aneurysms at autopsy. Blood pressure normal.
§ Blood pressure poorly controlled.
** One postoperative.
†† Discontinued hydralazine only.
‡‡ Attributable to drugs.

Changes in the Hypertensive State. Of the fifty-four living patients signs of the malignant stage are present in none. Three remain moderately hypertensive (Therapeutic Grade 3), twenty-seven mildly hypertensive (Grade 2), seventeen

pressure measured is shown in Figure 2, the single highest in each month being recorded. In Table III are indicated changes in blood pressure, renal function and non-protein nitrogen in blood in groups selected only in that accurate

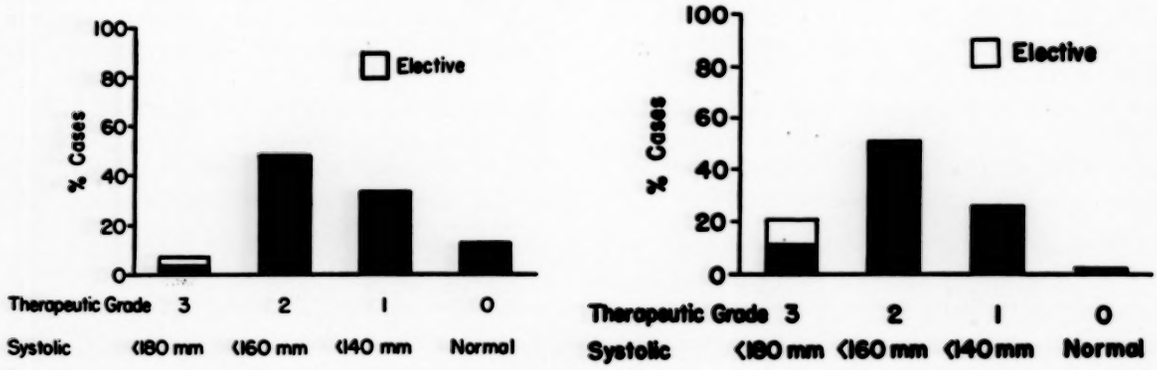

FIG. 1. Range of blood pressure in (A) 54 surviving cases of malignant (stage IV) and (B) 139 cases of severe "benign" (stage III) hypertension treated by hyphex, latest month of therapy. Elective signifies that a higher level was deliberately chosen in order to avoid renal insufficiency or cerebral vascular accident, or to prevent hypotension in patients with unsuccessful sympathectomy. Therapeutic grade of 3 corresponds to hypertension which could be considered as moderate, of 2 as mild, of 1 as "prehypertensive" and of 0 as normotensive (see text). Note that the results are better in malignant than in "benign" stages. These findings do not include the effects of added reserpine. For control ranges, see text. Results in stage II were comparatively better but are not shown, as this stage may respond to less specific measures. Patients in severe stages given only one drug almost uniformly attained a therapeutic grade of 3 or 4.

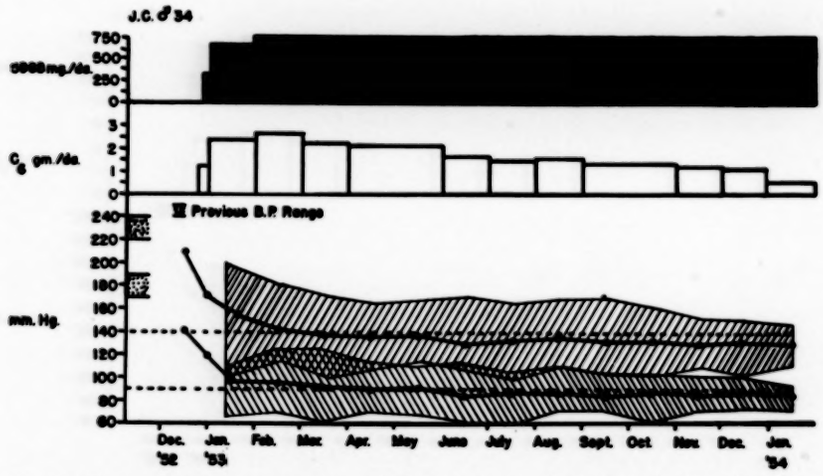

FIG. 2. Example of extreme ranges of blood pressure during treatment of malignant hypertension by hyphex. The doses of hydralazine (5968) and hexamethonium chloride (C_6) in gm. per day are indicated at the top; the average systolic and diastolic pressures are shown by the solid lines, each dot indicating 150 measurements except for the pretreatment levels, which indicate 42. The cross-hatched areas represent the lowest and highest reading obtained during each month as an outpatient (150 measurements). The range obtained by another physician during six months is indicated on the left. Ocular fundi were grade IV with visual impairment, albuminuria was 4-plus and renal function was borderline. He was able to return to work four months after discharge from the hospital, passing a thorough physical examination. At present he is asymptomatic; renal function has improved considerably and his ocular fundi appear normal. Note the gradual decrease in the hexamethonium intake required for control.

data were available for the exact week a year and two years following institution of therapy in each case, and all measurements of blood pressure were recorded for one and two years. Changes in the remainder were comparable but the data were only partly complete.

provement in the cerebral status so that drugs could be taken by mouth. Too rapid lowering of blood pressure in two cases apparently caused deepening of coma. Both recovered after lumbar puncture and decompression. One individual suffered three attacks, each one a day or two

TABLE III*

CHANGES IN SECONDARY EFFECTS OF HYPERTENSION (MEAN VALUES)

Function	Control	Two Weeks	Six Months	Twelve to Eighteen Months	Two Years	Subjects (No.)	Changing Unfavorably (No.)
Stage IVc:							
B.P. (mm. Hg)	223/140	.....	.....	169/98	156/94	13	0
Non-protein nitrogen (mg. per cent)	45	41	37	33	.....	..	..
Range	(30–90)	(17–90)	(20–90)	(20–89)	.....	20	2
P.S.P. excretion, % in 15/60 min.	3/18	5/22	7/28	8/30	.....	6	0
Stage IVb:							
B.P. (mm. Hg)	206/135	.....	.....	157/95	159/90	13	0
P.S.P. excretion, % in 15/60 min.	14/46	15/49	15/42	23/62	.....	10	2
Stage IVa:							
B.P. (mm. Hg)	206/130	.....	.....	160/94	148/89	6	0
P.S.P. excretion, % in 15/60 min.	13/55	12/50	15/51	23/62	.....	11	0
Stage III:							
B.P. (mm. Hg)	212/130	163/92	.....	156/94	155/90	10	0

* Patients were selected only in that records were complete for five recordings of blood pressure per day for the full period indicated. The exact week one year and two years after admission to hospital was used in calculations for mean blood pressure (thirty-five measurements). The control values were those obtained by nurses with the patient at rest (six per day, usually for one week). Because of the large number cases in Stage III were selected alphabetically.

It was necessary to discontinue 1-hydrazinophthalazine in five individuals (not included in the tables) with normal levels of blood pressure in whom late toxic reactions developed.[24] While the malignant stage has not reappeared, possibly because of massive doses of hexamethonium chloride, reserpine and, in some, protoveratrine, fluctuating hypertension has returned in every case and has become severe in four.

Deaths Directly Attributable to the Drugs. Four deaths were caused directly by acute interstitial fibrosis of the lungs; in another uremic individual this lesion was discovered. Hexamethonium ion is probably the initiating agent[10,12]

Effects in Cerebral Edema. Fourteen patients exhibited the complex of hypertensive encephalopathy (wet brain) with headache, vomiting, anxiety and convulsions progressing to or toward coma on admission to the hospital. Three were pregnant. The use of hexamethonium ion intravenously and intramuscularly to lower the blood pressure gradually resulted in sufficient im-

following poor cooperation in use of the drugs; another died of a recurrence when they were discontinued.

Present Occupational Status of Living Patients. The individuals in this group either had been incapacitated by their disease, had complained of visual disturbances or were urged by their referring physicians to enter the hospital because of obvious symptoms and signs suggestive of deterioration. At the time of writing, thirteen of the sixteen adequately treated living patients classified as Stage IVa had returned to full activity or employment and the other three to part time activity, limited by partial hemiplegia in two patients and old intraocular hemorrhage in one. Of those in Stage IVb, one was limited to part time activity and of those in Stage IVc, four were so limited. Of those who died from nonhypertensive causes while on full treatment (fourteen cases), two had returned to full activity, three to partial activity and nine were invalids. Seventeen azotemic individuals have lived more than twenty-two months.

Retinitis. In every adequately treated case ocular fundi of grades IV and III (Keith-Wagener) improved to grades II, I or became normal. Hemorrhages disappeared rapidly (within one to three weeks), papilledema less rapidly (two to six weeks), "soft cotton wool exudates" less rapidly (two to five weeks) and "hard exudates" very slowly (twelve to thirty months), shrinking gradually. Serial retinal photographs in color confirmed clinical observations.[3] Partial improvement was observed before discontinuation of the drugs was followed by death. No surviving patient with malignant hypertension shows retinopathy other than slowly disappearing "hard exudate" at the time of writing. The disappearance of the exudates resembles the gradual contraction of scars to tiny pinpoint white spots. The improvement was noted even in the presence of renal insufficiency. Acute edematous detachment of the retina disappeared rapidly (two to four days) in the four patients seen. No effect was observed in three patients with old massive intraocular hemorrhage with blindness.

RESULTS OF HYPHEX IN "BENIGN" HYPERTENSION

Mortality. The survivals and deaths of patients with severe hypertension are indicated in Tables I and II. Patients in moderate stages (II) considered candidates for hyphex were treated because of the presence of serious secondary complications (coronary arterial disease, congestive heart failure, cerebral vascular disease), primary organic renal disease with poor renal function, lesser signs of deterioration or severe headaches. One was treated in order that aneurysms of both popliteal arteries could be successfully repaired surgically.

Minor Changes. Subjective improvement was sufficient so that 162 patients continued to stay on a rather rigid regimen of pill-taking and measuring blood pressure, without excessive urging. Objective improvement in the state of the ocular fundi of grades II and I was frequently noticed. As expected, dilated cardiac shadows in roentgenograms became smaller, although those of patients without congestive heart failure, which were only slightly enlarged, changed very slowly or not at all. Disappearance of the "strain pattern" in the electrocardiogram was frequently found; alterations due to coronary occlusion were uniformly unaffected. Pulsations in the arteries of the feet, usually small in hypertension, increased to normal amplitude. Renal function as measured by the fifteen-minute urinary excretion of injected phenol red, when normal, was unchanged or increased; when reduced, often became further reduced initially only to return to normal values in one to two years time. Albuminuria when not secondary to primary renal diseases uniformly diminished or disappeared. In a few, the characteristic electroencephalographic fast dysrhythmia[3] appeared to regress.

Unsuccessful Sympathectomy. In sixteen patients lumbodorsal and in two thoracic sympathectomy had been performed one to six years previously; severe hypertension had returned in all and serious secondary complications had occurred in ten. Five were in malignant stages, two with renal insufficiency. A therapeutic Grade of 3 was elected in two cases while three patients eventually attained a Grade of 2 without postural hypotension. In thirteen patients severe benign hypertension was present with blood pressure markedly elevated in the erect position; an elective Grade 3 response was chosen in two, while eight were classified as Grade 2, one as Grade 1 and one became normotensive. One patient died of a second attack of apoplexy. It was common to observe gradual decrease in resistance to the drugs during twelve to eighteen months.

CHANGES IN THE SECONDARY EFFECTS OF HYPERTENSION*

Congestive Heart Failure. Eighteen living patients had suffered from congestive heart failure before therapy was instituted. Digitalis and diuretics became unnecessary after elevated blood pressure was controlled and dietary salt was later not restricted. All but one returned to full activity without recurrence of decompensation. One patient previously in malignant stages and totally incapacitated passed a physical examination for life insurance after fifteen months of treatment. Two of the controls suffered from arteriosclerotic heart disease; lack of cooperation in one was associated with continuation of failure, while in the other failure persisted both on and off therapy. The death rate, however, was high, for eleven continuing treatment have died; three of cerebral arterial thromboses, two of progressive uremia, two of interstitial pneumonia and four of unknown causes while

* The cases and deaths discussed in this and subsequent sections are a recapitulation of those summarized in the previous section.

normotensive. Twenty were in malignant stages (ten deaths) and nine had renal insufficiency (five deaths); twelve were in benign stages (two deaths). Although a cardiac cause of death was not established in any, coronary occlusion may have occurred in one or more of those dying without autopsy.

accidents before therapy was begun. After arterial hypertension was controlled, one of these experienced a minor recurrence lasting two weeks, apparently induced by several days of hypotension. (Table IV.)

In other patients cerebral vascular accidents, however, were not prevented by control, espe-

TABLE IV

INCIDENCE OF NON-FATAL HYPERTENSIVE COMPLICATIONS IN 211 PATIENTS ON THERAPY THIRTEEN TO THIRTY-FOUR MONTHS (ALL STAGES)

	Present before Therapy	Recurrence in Same Patient	First Appearance					
			IVc	IVb	IVa	III	II	Total
Uremia developing*	20	0	..	..	..	..	..	0
Congestive heart failure	18	1	..	..	..	..	..	1
Cerebral hemorrhage	41	0	..	..	..	..	..	0
Cerebral arterial thrombosis		0	..	2	2	..	..	4†
Cerebral edema	14	0	..	..	..	..	..	0
Coronary occlusion	33	1	..	..	..	3	..	3
Angina pectoris	9	1‡	..	..	..	1	..	1
Transient cerebral angiopathy	12	0	..	..	..	2	..	2

* For example, in patients initially with nitrogen retention.
† Aphasia in two; recovery without residual in three.
‡ Rare attacks since.

Coronary Arterial Disease. Thirty-five patients had suffered a coronary occlusion before treatment was begun. One died suddenly while at work and one has had a recurrence. One discontinued treatment and died. Further attacks have not occurred in the remaining thirty-two. In four other cases transient electrocardiographic changes developed during induction of control, such as bundle branch block and signs suggestive of subendocardial myocardial ischemia, which disappeared. On the other hand, initial attacks of coronary occlusion were not prevented by control of blood pressure, for three non-fatal and three fatal episodes occurred. (Table IV.) In the smaller control group there were three deaths and two non-fatal attacks. Sudden deaths, possibly of cardiac cause, occurred three times in the treated patients and ten times in the controls.

Ten patients suffered from angina pectoris. One discontinued treatment and is unrelieved. Eight are asymptomatic and one requires nitroglycerine for pain about once a month as compared to the former needs of six to eight times a day.

Cerebral Vascular Disturbances. Forty-one patients suffered one or more cerebral vascular

cially when malignant stages had been present. In two patients partial aphasia developed during induction of therapy; both recovered. A young woman became hemiplegic after six months of therapy. A man suffered three minor accidents (thromboses) after ten months and died. Transient hemiplegia developed in an elderly woman with cerebral atherosclerosis. An elderly man with similar changes, but in benign stages, died of apoplexy probably due to thrombosis. Fatal cerebral hemorrhage occurred in two patients. The blood pressure of a fifty-five year old man in benign stages was poorly controlled. He died after eighteen months of therapy and at autopsy extensive atherosclerosis was found. A young Negro woman formerly in Stage IVc with congestive failure died of a cerebral hemorrhage while normotensive. At autopsy three cerebral arterial aneurysms were found, one of which had ruptured.

Twelve patients exhibited symptoms and signs of cerebral atherosclerosis and softening. One discontinued treatment and died of apoplexy within a month. Four others were discontinued for lack of cooperation. The neurologic condition of the remaining seven is unchanged.

Effects of Hyphex on Other Bodily Functions. A number of studies have been made in order to determine whether or not these drugs cause disturbances of other functions of the body. The level of total plasma cholesterol was observed to fall moderately in almost every case (average 46 mg. per cent or more) for several months, rising again at a year's interval. In a number a normal level of non-protein nitrogen in the blood was reduced to quite low values (10 mg. per cent). Function of the liver as measured by the retention of bromsulphalein,® thymol turbidity of the serum and cephalin-cholesterol flocculation was unchanged after three to twelve months on treatment unless toxicity to hydralazine developed.[24] Pyruvic acid and total carbonyl levels in the blood were unaffected. Levels of fasting blood sugar and tolerance of the blood sugar to ingested glucose were unaltered; the severity of diabetes mellitus in two cases was unchanged. The basal metabolic rate was unaltered except in a few cases in which a low rate rose to normal values. Body weight was uninfluenced; several individuals gained considerable excess fat but none lost weight without dietary restriction. A six year old child developed and grew normally during two years. However, no live infants have been born to pregnant women in these studies; therapy was not begun until pregnancy was complicated by toxemia, but one woman became pregnant and was delivered of a normally developed premature infant who lived only thirty hours. No signs of hypo- or hyper-adrenocorticalism have appeared; the endocrine disturbance of two exhibiting Cushing's syndrome was unaffected although the malignant stage of

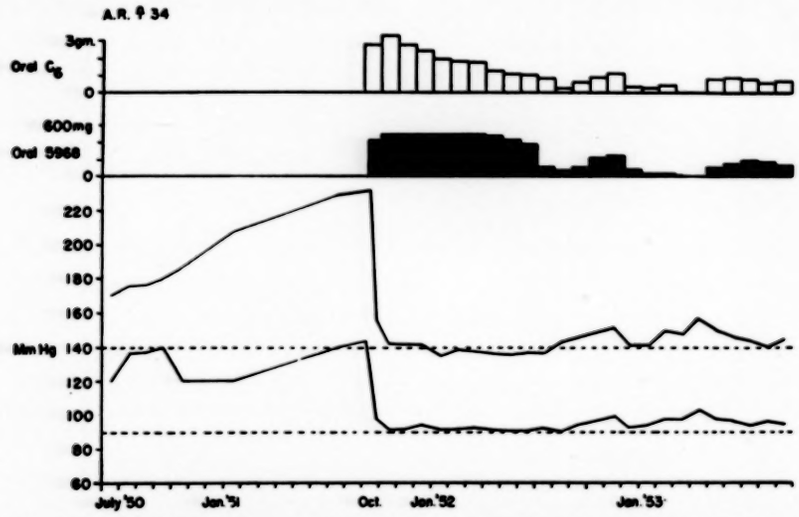

FIG. 3. Alterations in dosage of hyphex during prolonged treatment. A. R. was an intelligent thirty-four year old white woman suffering from right pyelonephritis for twelve years and severe benign hypertension for at least two. In 1950 her diastolic pressure varied from 120 to 140 mm. and her systolic from 170 to 210 mm.; in 1951 her systolic pressure varied from 200 to 230 and her diastolic from 120 to 140 mm. on seven visits to her physician. On admission to the hospital her systolic pressure was as high as 240 and her diastolic 160 mm. with an average during a week of 211 and 127 mm. Her heart was enlarged and her right renal pelvis distorted on pyelography. Control was excellent. The doses of each drug were gradually diminished because of sustained normotension. In October, 1952, she suffered an attack of pyelonephritis, which may or may not have been responsible for the rise in the weekly average pressure. She has remained symptom-free, takes no laxatives, enjoys no restrictions on her activities and has handled herself extremely well. During April and May, 1953, she took no drugs; her diastolic pressure slowly became elevated to as high as 130 mm. on one occasion, requiring return to the drugs. She was able to discontinue them again a year later without elevation of blood pressure occurring for two months; how long this will continue is questionable. Undoubtedly some underlying process has been reversed. Each point on the chart represents the average pressure for one month (at first five readings a day, later three a day). C_6, average daily dose of hexamethonium chloride; 5968, average dose of 1-hydrazinophthalazine.

hypertension regressed. Except in late toxic reactions no changes have appeared in the concentration or distribution of white blood cells. the number of platelets or the sedimentation rates of erythrocytes, nor were the concentrations of albumin and globulin in plasma altered.

1.78 gm. at the end of a year; in ten of these, followed for two years, it further decreased to 1.35 gm. The average daily dose of hydralazine, reduced by us only because the patient was showing sustained normotension, decreased from 0.52 to 0.49 gm. and after two years to 0.31 gm. A few

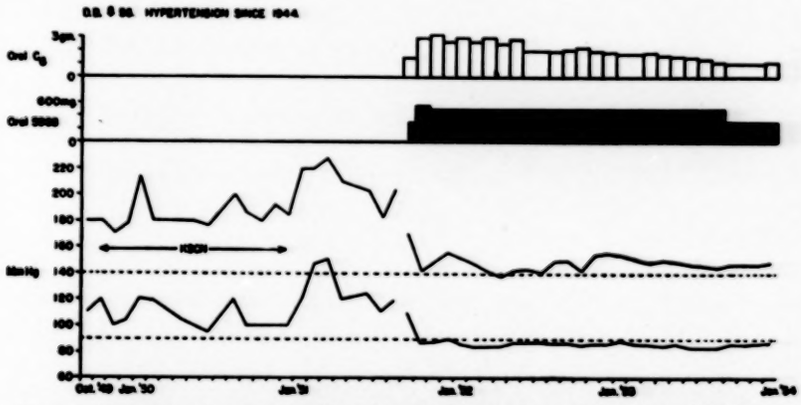

FIG. 4. Alterations in dosage of hyphex during prolonged treatment. D. B. was a fifty-six year old woman with severe neurogenic and renal hypertension which had progressed to cardiac and borderline renal insufficiency. She had been bedridden for three months because of congestive heart failure. For three years she was under the care of Dr. Samuel B. Grant, who saw her repeatedly and administered potassium thiocyanate in full therapeutic doses with the effect shown. On admission to the hospital in October, 1951, she was in moderately severe congestive failure. Her ocular fundi were grade III. Her kidneys were able to excrete only 5 per cent of injected phenol red in fifteen minutes, and there was 4-plus albuminuria. Non-protein nitrogen in her blood was 34 mg. per cent (Somogyi-zinc method). After control was instituted, the non-protein nitrogen fell to 17 mg. per cent and the fifteen-minute excretion of phenol red rose to 20 per cent. Albuminuria disappeared completely, cardiac compensation was restored and digitalis was discontinued. During treatment monthly averages of blood pressure are shown, each point representing 150 measurements. Note the progressive fall in the dose of hexamethonium chloride made necessary by the "self-eliminating" schedule.

Mild secondary anemia, perhaps a reflection of the affinity of the hydrazines for ferric iron,[16] occurred during the first month or two of hyphex in most patients, disappearing without treatment. The concentration of red blood cells did not fall below 3.5 million per cu. mm. and usually remained above 4.0 million. After a year of therapy no anemia has been discovered except in cases with late toxic reactions. The sulfhydryl content of urine, diminished in hypertension,[28] decreased to lower values.

REDUCTION IN DOSAGE

After six months to a year on hyphex therapy the amount of drugs required to maintain control of blood pressure has decreased significantly. The average daily dose of hexamethonium chloride, taken by the first thirty cooperative patients analyzed, decreased from 2.08 to

individuals have reduced their dosage to very small quantities. Patients apparently quite resistant to therapy (Grade 3) have uniformly developed normotension on readmission to hospital a year or two later. (Figures 3 and 4).

Mishandling. While tolerance to the drugs has not appeared when they were properly administered, temporary discontinuation during induction of control in cases of malignant hypertension has been followed by resistance to subsequent administration. In ten individuals the agents were so mishandled, often because of minor or distressing side reactions which were not treated specifically. Five died of progressive uremia during the initial hospital admission; three had exhibited nitrogen retention. Control was achieved with great difficulty in one, and four remained partly resistant. We are at a loss to account for this phenomenon. Similarly, pa-

tients insufficiently treated for long intervals have sometimes appeared more resistant than untreated ones. When "tolerance" was allowed to develop by insufficient dosage, reduction of blood pressure became very difficult.

Toxic Reactions. The late toxic reactions due to hydralazine have been reported in full.[3,10,24,25] The incidence in this series was 8.1 per cent. Likewise reactions occurring as a result of lowering of the blood pressure have been documented.[3,10] No other types have been encountered since these reports were published. Four deaths directly due to interstitial fibrosis of the lungs have occurred.[10]

Practicality of Method. In twenty-six cases one or both drugs were discontinued by or on the advice of a physician; death resulted in half. Generally minor side effects due to hexamethonium ion was given as the reason, although in four cases the drug could not be tolerated owing to the presence of partial organic obstruction of a hollow viscus. Treatment was discontinued voluntarily at home by the remainder (thirty-eight patients), an incidence of failure to cooperate of 12.7 per cent. Negro women were less cooperative than others, five having failed to continue voluntarily as compared to one Negro man. However, ward patients were no less inclined to continue treatment than private patients. For all reasons in white patients one or both drugs were stopped in the cases of twenty-two private and three ward men, twenty private and nine ward women; in Negro patients, in the case of two men and eight women. Three women discontinued both drugs because of the appearance of sustained normotension. As in the control of diabetes mellitus with insulin and diet, failure of cooperation, lack of intelligence and poverty limited the effectiveness and practicality of this method of control of hypertension.

EFFECT OF OTHER AGENTS AND COMBINATIONS

Reserpine. Our experiences with reserpine and less purified alkaloids of Rauwolfia serpentina confirm those of Wilkins,[5] i.e., that hypotensive action of mild potency was observed. Although cases have been followed for too short a time to allow definite conclusions as to the eventual effect of this drug upon the disease, blood pressure has fallen to normotensive levels and remained there by casual measurements in about half of twenty patients in Stage I; patients recently treated in Stage II have required the addition of hydralazine to control the hypertension (eighteen cases). Only a rare individual referred to the Hypertension Clinic has benefited significantly from these agents used extensively and several have suffered progression of their disease.

Reserpine (1.0 mg. per day) was added to hyphex in seventy-five cooperative patients in severe "benign" stages. In approximately one-quarter an effect could be observed in that the daily dosage of hexamethonium chloride was automatically reduced. (Figs. 5A and B.) The remainder noticed no change.

In seventeen individuals hydralazine was discontinued because of late toxicity.[24] Hypertension returned in all despite large doses of reserpine and considerable increases in the dose of hexamethonium chloride; in some cases protoveratrine given to the point of vomiting had little prolonged effect. Three deaths from hypertensive complications have occurred in this group with partly controlled blood pressure levels.

Protoveratrine. We have been unable to control the blood pressure at reasonable levels for the full twenty-four hours with this agent. Wide swings from hypotensive to hypertensive ranges have been observed; maintenance therapy was therefore impossible. Measurements taken at the same hour after a dose, however, gave false impressions of efficacy; when readings were made every four hours, hypertension reappeared for a considerable portion of the time. The addition of this agent to hydralazine and reserpine, however, appeared to be effective in a few individuals unable to take hexamethonium chloride. (Figs. 6 and 7.)

Pentapyrrolidinium Bitartrate. This agent was substituted for hexamethonium chloride in twenty-two individuals. Preliminary observations suggest that it may be somewhat more effective in providing control. In five cases the results were unequivocal.

Single Drugs. Hexamethonium chloride administered orally in full doses has been given alone for long periods to eight individuals unable to tolerate hydralazine initially; no better than a Grade 3 or 4 therapeutic response was observed when blood pressure was measured in the sitting position. The dose was not further increased as tolerance developed. Hydralazine alone was given to seventy individuals and the responses were significant but similar.[23] Patients treated with this agent in the past two years have shown

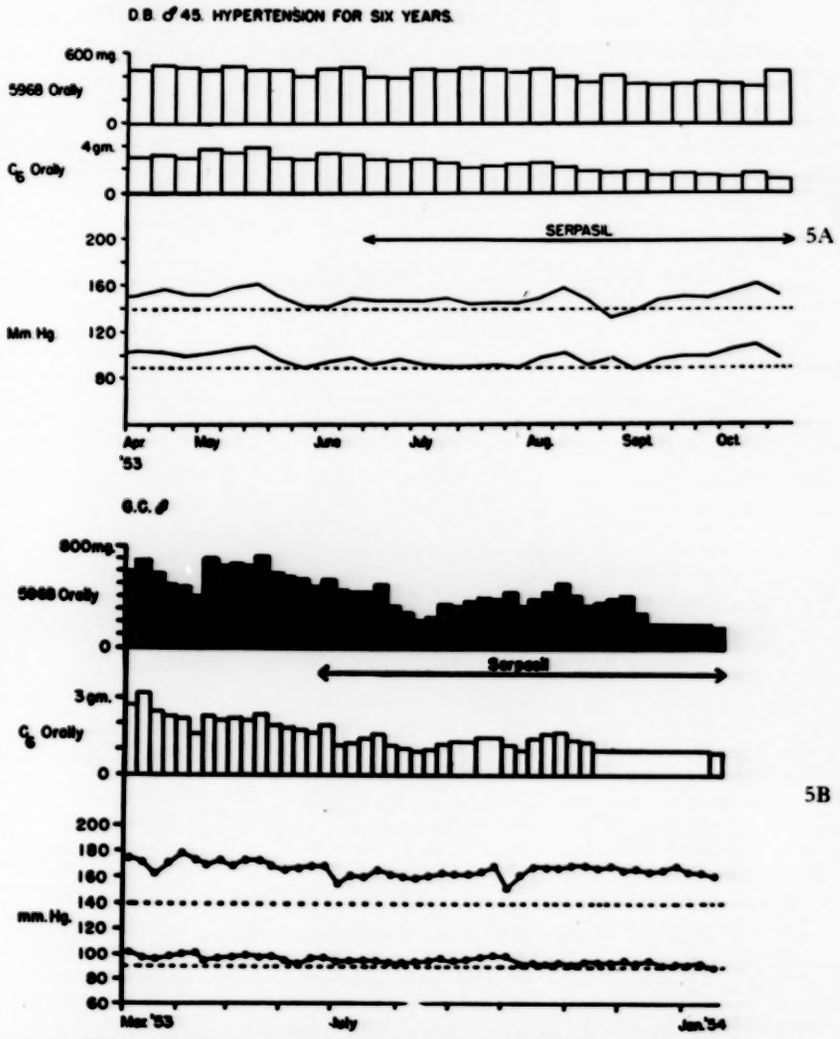

FIG. 5. Effect of added reserpine. A, average weekly blood pressure levels (each 35 measurements) and average daily doses of hydralazine (5968) and hexamethonium chloride (C_6) as affected by reserpine (serpasil) 1.0 mg. per day in a patient with severe "benign" hypertension previously suffering from congestive heart failure. He had been on treatment for two years with a fair response (grade 2 to 3), his pretreatment levels ranging between 200 and 250 systolic and 130 and 150 mm. Hg diastolic. Congestive failure had disappeared without drugs or dietary restrictions. Note the decreased intake of hexamethonium chloride required when reserpine was added; the average level of blood pressure appeared to rise at the end of the period. B, same in a fifty-four year old man with severe aortic atherosclerosis who after one year achieved only a grade 3 response from initial levels of 205 to 240 systolic and 120 to 140 mm. Hg diastolic. He preferred to maintain his blood pressure at levels higher than normal and to vary his dose of hydralazine; his diastolic pressure was only slightly elevated. Note the reduction in average daily dosage of both agents without change in blood pressure when reserpine, 1.0 mg. a day, was added. Control had been previously increased on two occasions by adequate doses.

relatively poor results (three of ten have died and two others suffered apoplectic strokes).

COMMENTS

When an effective method of control of a disease with strong psychogenic influences is developed, the utmost test of the method and a severely critical analysis of the results are imperative. These we have attempted. Many years of experience with many drugs and surgical procedures have convinced us that the present method is more specific and more effective in controlling hypertension than any other of which we are aware, for all cases responded to therapy. To be able to teach cooperative patients with severe and malignant hypertension to control blood pressure at mildly hypertensive or normotensive levels in all but 11 per cent of cases denoted that the method is effective. Its specificity is suggested by its ability to reverse the malignant stage, cause gradual improvement in renal function, become increasingly effective

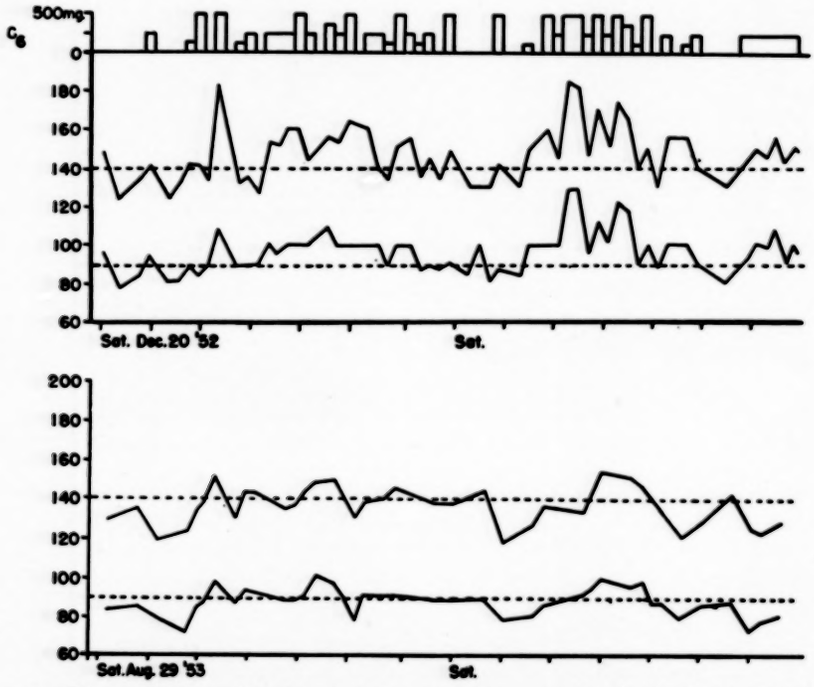

FIG. 6. Example of partial control of neurogenic hypertension by hyphex and excellent control later by the addition of other drugs. Daily fluctuations in blood pressure of J. P., a forty-three year old wholesale grocery merchant, who exhibited "hypertension every Monday." *Top curve:* His highly competitive business activities were confined to the first three days of each week when he was under excessive emotional tension. The dose of hexamethonium chloride varied from none on weekends to 2.0 gm. a day on Mondays. During vacations he had suffered from sustained hypotension. When these readings were made, he had been taking hyphex for sixteen months and the pattern was consistent. The Christmas season, a busy one for him, is included. Emotional tension caused by his business activities probably accounted for the weekly rise. In his case the course of hypertension was modified but the disease was only partly controlled. The dose of 1-hydrazinophthalazine was 500 mg. per day. *Lower curve:* Five months later he was given protoveratrine 0.8 mg. a day and raudixin (Rauwolfia serpentina) 100 mg. a day instead of hexamethonium ion. His emotional responses were probably blocked, his variations in blood pressure remaining as shown. The dose of hydralazine was 400 mg. per day. He had exhibited severe benign hypertension when examined at the Mayo Clinic in July, 1951, where his systolic pressure was 250 mm. and his diastolic 150. Similar levels discovered by us, were altered downward somewhat with rest in bed. He had suffered three "strokes" with residual weakness of his right arm. This improvement continued for six months on 300 mg. of hydralazine per day without protoveratrine.

after a year or more and allow the patient a return to a state of health consistent with atherosclerotic and renal changes previously present.

While the usual aim of treatment or control of any abnormality is a return to a normal state, arterial hypertension has been considered an exception. A large body of opinion was concerned with the belief that an elevated blood pressure, once established, was "essential" to the maintenance of adequate blood flow through vital organs. Therefore, control of blood pressure at lower levels was thought to be "unphysiologic" and might be harmful.

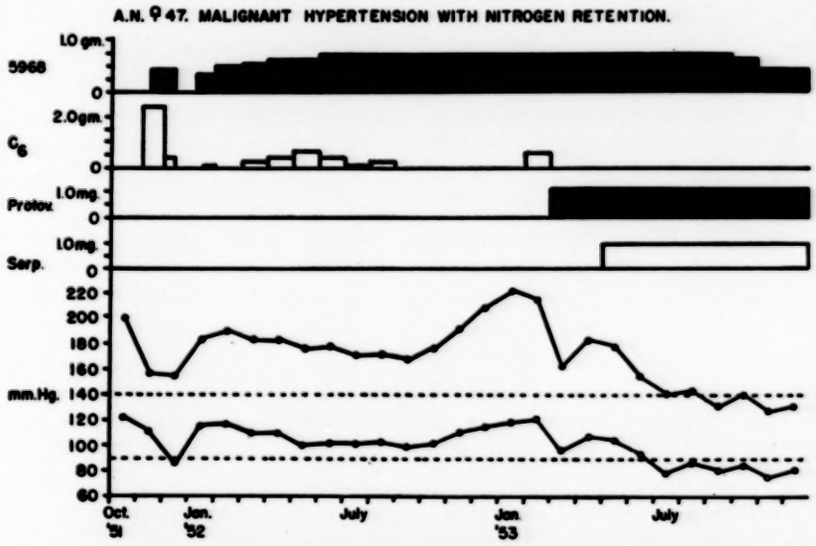

FIG. 7. Example of poor initial control of blood pressure by insufficient doses and excellent control later in a patient with malignant hypertension and renal insufficiency who also suffered from partial asymptomatic duodenal obstruction. Hypertension of ten years' duration had become severe and grade IV ocular fundi had developed. She had suffered a minor apoplectic stroke. Hexamethonium chloride induced intermittent subtotal obstruction and vomiting and was poorly tolerated after two months. After the initial excellent response, a grade of only 3 or 4 was achieved on large doses of hydralazine; one year later blood pressure slowly returned to control levels. The addition of protoveratrine caused a sharp decline to grade 3 levels; the later addition of reserpine (serpasil) produced normotension. Each point represents the average of 150 measurements. Elevated non-protein nitrogen in her blood of 40 mg. per cen t(Somogyi-zinc method) had fallen to 16 mg. per cent, an abnormal electrocardiogram had become normal, and her ocular fundi had cleared. In our experience the effect of these two additional agents in severe stages is unusual. This case is illustrative of the point that control of hypertension is possible in almost all cases.

The present study in part disproves this belief. The theoretic dangers of normotension, i.e., coronary and cerebral arterial thrombosis, renal insufficiency and mesenteric thrombosis have been much less than believed at the outset. While it is true that atherosclerotic individuals may feel somewhat uncomfortable at normotensive or slightly hypertensive levels during the first few months of therapy, after a year or more many have remarked upon their ability to tolerate increasingly lower levels without symptoms. Since only generalized vasospasm is being treated, the contribution of that alteration in severe hypertensive states must be relatively much greater than formerly believed and the organic vascular disease much less. We have no direct evidence in this short study that the latter component is reversible.

The results of hyphex summarized herein are in general better than most reports in the recent literature relating to the use of one or both agents. A careful analysis of the methods employed has usually revealed one or more of the following reasons for the discrepancy: (1) The apparent rapid excretion rates of both hydralazine[3,20] and hexamethonium ion[3,9,29] requiring doses at four-hour intervals has escaped attention. In order to lower blood pressure we have found it necessary initially to give both drugs

every four hours around the clock. When normotension has been established, it has been possible to omit one dose in the middle of the night; however, even this alteration has almost invariably resulted in a moderate rise in the "resting" blood pressure level each morning. Eventually, many of our patients achieved control with medication every five or six instead of every four hours, but this reduction was unpredictable, slow to occur and required full cooperation for many months. (2) The dose of hydralazine was insufficient to produce the effect desired and was not maintained at a constant level regardless of the blood pressure. All of our patients in Stages III and IV have required 600 mg. a day or more during induction of control and 500 mg. a day or more for six to twelve months thereafter; in the most severe types the maintenance dose has ranged from 750 to 1,000 mg. We have yet to encounter a patient in whom blood pressure could not be significantly lowered, although the wisdom of causing such alterations in uremic states and acute apoplectic strokes might be questioned. The general impression was gained, however, that male patients in the sixth decade in benign stages exhibiting aortic atherosclerosis were partly resistant to therapy and required large doses. (3) The hexamethonium dosage was inadequate. All patients in severe and malignant stages have required 2.5 gm. of hexamethonium chloride a day and a number have required more (3.75 and, in rare cases, 5.0 gm.). (4) The necessity for frequent measurements of blood pressure before each dose, not only to avoid hypotension but also to provide an amount of hexamethonium ion sufficient to produce normotension for the next four hours has not always been observed. Because of the unpleasant symptoms of hypotension there is a tendency for a patient to underestimate his requirement when he does not take his pressure. (5) Patients have been insufficiently educated to control their own levels of blood pressure or were of insufficient intelligence to do so. For example, in a series of eleven patients treated at the St. Louis City Hospital, the data of which we have analyzed, only five good results were found.[30] Similarly, Galen and Johnson[31] reported four failures in thirty-six adequately treated clinic outpatients following our method but not recording blood pressure levels at home. (6) Moderate reduction of blood pressure and not normotension has been the aim of therapy. With the exception of a relatively small number of individuals with unsuccessful lumbodorsal sympathectomy, advanced atherosclerosis or severe renal insufficiency, our patients have been taught to reduce or omit doses of hexamethonium chloride only when the systolic pressure was 140, 130 and 120 mm. Hg in the sitting position. It has been our strong impression that those patients who have achieved normotension have had less subsequent trouble regulating their pressures, have suffered from fewer side effects and have done better in general. (7) The physician discarded therapy before adequate control was established. We have seen patients who have been partly resistant for many months later become more susceptible to the drugs. An occasional one with severe malignant hypertension has achieved relative normotension only after a year or more of vigorous therapy. (8) The dose of one or both drugs was not increased later when the individual had achieved only a Grade 3 response. The aim of treatment was normotension; while not always achievable, adjustment of dosage became necessary when an improving trend was not demonstrable at the end of six to twelve months.

Conversely, a number of favorable reports have appeared in which profound effects have been observed with the sole use of hexamethonium ion or, less often, hydralazine. Our experience with patients in severe and malignant stages is unconfirmatory.[23] Recording of standing pressure levels, infrequent measurements made during the daytime after a dose, a preponderance of milder cases, comparison of physicians' records, may account for this discrepancy when hexamethonium ion was given; deaths from hypertensive complications in one series, for example, were large and even included pulmonary edema,[32] a condition which we have not encountered. However, the occasional favorable response to hydralazine alone in malignant hypertension is noteworthy.

Rather than average the enormous number of measurements of blood pressure in our data, we have preferred to grade the present status of each patient according to the criteria discussed in this report. These standards are indices only of the severity of the hypertension while under treatment; the previous status of each patient can then be compared. More attention is therefore placed upon the range of blood pressure before and after treatment than upon single readings, which usually give false impressions. Furthermore, levels obtained by nurses with

the patient at rest in the hospital are compared with levels obtained by the patient or a member of his family under conditions of full activity, thus lessening the numerical change which would be manifest if physicians' measurements were considered as controls. The blood pressure varies considerably from hour to hour under treatment, attesting to the unevenness of action of the drugs and of the emotional status of the patient.

We have also not recorded percentage changes in blood pressure, an erroneous method of analysis as simple calculations readily indicate. The average per cent change in fifty consecutive patients with severe "benign" hypertension was 33/29 from an initial level of 228.1 and 131.5 mm. Hg. Obviously the percentage fall of systolic pressure would be the same from 300 to 200, 210 to 140 and 180 to 120 and of diastolic from 180 to 128, 130 to 92 and 100 to 71, but in the first instance the patient remains hypertensive and therapy has been relatively ineffective.

Changes in some of the secondary effects of increased intra-arterial tension could have been predictable in the light of the altered hemodynamics of hypertension: the disappearance of congestive heart failure when cardiac work was diminished, shrinkage of dilated hearts, reversal of the electrocardiographic strain pattern, relief of dyspnea and left ventricular failure (suggesting that Starling's law of the heart is applicable to the left ventricle). Less predictable was the slow improvement in renal function, the regression of proteinuria and the fact that nitrogen retention did not develop when it had not been present before treatment. Unpredictable was the rapid disappearance of acute hemorrhagic and exudative lesions in the ocular fundi and especially the absorption of "hard" exudates. These reversals indicate their dependency either upon an elevated blood pressure or upon some associated metabolic abnormality altered by one of the drugs.

Considering the clinical material used in this study, the high gross mortality rate in the 212 patients with severe and malignant hypertension adequately treated (9.0 per cent) is not disturbing. All cases, no matter how serious, were treated. Errors in administration of the drugs were made initially during the pioneering stage. When the mortality rates of groups are examined carefully, however, one finds the following: gross mortality of patients discontinuing treatment, 60.9 per cent; mortality due to known hypertensive complications of patients excluding those who presented themselves in uremia or severe renal insufficiency, continuing treatment 3.2 per cent, discontinuing treatment 55.0 per cent; mortality, non-hypertensive causes, continuing treatment, 5.3 per cent, discontinuing treatment 3.1 per cent. That all twenty-two patients in severe malignant stages who failed to continue full treatment died of the acute effects of hypertension while of all sixty-eight continuing only three died, serves as an unfortunate but convincing self-selected control. Furthermore, there were only five deaths due to acute hypertensive causes in the 144 patients with severe benign hypertension, while nine occurred in the twenty-eight failing to continue. Also not surprising are the five deaths of non-hypertensive causes occurring in patients in severe malignant stages with renal insufficiency. The vascular systems of these individuals were markedly damaged; a third had been in heart failure, one had suffered two or more cerebral vascular accidents and one had exhibited cerebral edema three times.

The seriousness of the secondary changes present in these patients becomes obvious when each is graded according to the criteria of Smithwick[33] which includes the effects of atherosclerosis. All patients in Stages IV and III were in his Groups 4 and 3. Of those in Stage II, seven were in Group 4, thirteen in Group 3 and six in Group 2. The one-year mortality rates of patients treated medically according to Smithwick are: Group 4, 50.5 per cent; Group 3, 17.2 per cent; Group 2, 9.6 per cent. For surgically treated patients (lumbodorsal sympathectomy) they are: Group 4, 23.6 per cent; Group 3, 4.6 per cent; Group 2, 3.3 per cent. While the two-year mortality rates of patients adequately treated by hyphex is somewhat lower than that of those surgically treated for one year, the temporary improvement is most obvious in patients with renal insufficiency.

Disturbing, however, are the four deaths from interstitial pneumonia and that finding in another at autopsy. We are at a loss to explain why four of these occurred in Negroes, why all had been in malignant stages and why progress was so rapid.[10] The rarity of interstitial pneumonia as a cause of death makes it reasonable to implicate one of the drugs.[34]

Equally disturbing are the late toxic reactions resembling disseminated lupus erythematosus

and rheumatoid arthritis. 1-Hydrazinophthalazine and its derivatives were definitely of etiologic significance, repeatedly causing fever and recurrence of acute arthritis. Fortunately the condition has responded rapidly to cortisone and discontinuation of the offending drug. We can predict with fair accuracy that these late reactions will increase in frequency.

Neither of the two drugs used is ideal. Hexamethonium chloride administered orally appears safe only when precautions are taken to prevent constipation and hypotension. The action of the drug is not truly "specific" in that unwanted parasympathetic inhibition is produced. At present, however, no sympatholytic drug known to us replaced hexamethonium ion without causing distressing tachycardia and other intolerable symptoms. It is hoped that such an agent will be discovered. The hydrazine derivatives are also far from ideal in that late toxic reactions and new diseases are caused by them. Depletion from the body of essential trace metals may result for they have a strong affinity for cupric, stannic and manganous ions and reduce ferric and pervanadate.[16] They are effective antihypertensive agents only in combination with other drugs which act upon the autonomic nervous system. Because of late toxic reactions, hyphex represents a "calculated risk" worth taking when hypertension threatens life and health but not to be taken when the disease is in milder stages and other agents are effective. While by no means ideal, therapeutic agents now available and employed intelligently represent first approximations of effective methods for medical management of most cases of hypertension. Although control of hypertension is now practical, it is hoped that new and more effective methods will appear.

SUMMARY AND CONCLUSIONS

Methods effective for medical control of the elevated blood pressure of arterial hypertension are now available; one such (hyphex) has been used in 304 consecutive patients selected only as representing the more severe forms of the condition. The mortality rates from hypertensive causes in malignant hypertension adequately treated during thirteen to thirty-four months were: with previous uremia, 100 per cent; with renal insufficiency, 11 per cent; without renal insufficiency, 3 per cent; of those discontinuing treatment 89 per cent died. The mortality rate from hypertensive causes in severe benign hypertension adequately treated was under 4 per cent; of those discontinuing treatment 32 per cent. The mortality rates from non-hypertensive causes including that due to drugs were: malignant hypertension, 16 per cent; benign hypertension, none. Severe benign and malignant hypertension regressed into mild or moderate stages in all cases adequately treated. Limits of effectiveness of the method lay in renal insufficiency. While not ideal, the method was safe when precautions were taken and the patient was carefully instructed. Less potent agents were effective in less severe stages of the disease. The three most useful oral drugs were hexamethonium chloride, hydralazine and reserpine; combinations of two or more were required for adequate control of hypertension in all but the milder stages. It is concluded that one or more agents which affect the autonomic nervous system must be combined with a drug which affects vascular smooth muscle or renal enzymatic mechanisms for severe stages of arterial hypertension to be controlled adequately.

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Clinico-pathologic Conference

Fever, Lethargy, Pericarditis and Sudden Death

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. M. (History No. 231001), a seventy-eight year old housewife, entered the Barnes Hospital on January 6, 1954, complaining of fever of one week's duration and pain in both eyes for three hours prior to admission. The patient had enjoyed excellent health all of her life. At seventy-three she was found to have mild diabetes, controlled by diet alone. Three weeks before admission she noted marked fatigue, irritability and increasing anorexia, all of which she attributed to the stress of preholiday activities. Seven days prior to entry she became lethargic and complained of occasional chilly sensations. A few days later she was found to have a fever of 102°F. Her physician treated her with oxytetracycline, but she remained febrile with daily elevations to 103°F. The lethargy persisted unchanged. Approximately three hours prior to entry she awoke with severe pain in both eyes, an intense frontal headache most marked on the left and photophobia. Shortly thereafter, while walking in the bathroom with her eyes closed, she fell into the bathtub and struck the back of her head. She could not say whether she lost consciousness after the accident, but she was brought immediately to the hospital.

The past history indicated that a hearing defect had been present for years, necessitating the use of a hearing aid. Fifteen years prior to admission the patient was hospitalized for repair of a cystocele. She was known to have chronic sinusitis and two years prior to admission had herpes zoster of the neck. Her family history was significant only in that her mother had had diabetes.

Physical examination at the time of admission revealed the patient's temperature to be 37.5°C., pulse 116, respirations 16 and blood pressure 156/80. She was an elderly white woman lying in bed with her eyes closed and wearing dark glasses. She complained of photophobia and severe pain in the eyes. Her skin was warm and smooth, and there were small red herpetic scars on the neck. The bones and joints appeared normal. No enlargement of lymph nodes was noted. There was a small abrasion of the scalp over the left occipital area covered with dried blood. The conjunctivae were injected and there was minimal purulent exudate on the left. The fundi were poorly visualized. The trachea was in the mid-line. The thyroid was not enlarged and no masses were felt in the neck. The neck was supple and there was no deformity or tenderness of the back. There was moderate increase in anteroposterior diameter of the chest. Percussion note was resonant; crackling rales were heard at both bases posteriorly. The heart was not enlarged to percussion and there was a normal sinus rhythm. The first mitral sound was split, A_2 was greater than P_2, and grade 1 systolic murmur was heard at the base. The abdomen was protuberant but no organs were palpable, nor were there any masses or tenderness. Bowel sounds were active. Pelvic examination was within normal limits. The rectal sphinctor was lax. Neurologic examination was within normal limits.

The laboratory data were as follows: hemoglobin, 10.6 gm. per cent; white blood cells, 11,450 per cu. mm.; differential: segmented neutrophils, 66 per cent; non-segmented neutrophils, 4 per cent; lymphocytes, 30 per cent. Urinalysis: specific gravity, 1.017; albumin, trace; sugar, 4+; acetone, negative; centrifuged sediment, 2 to 4 white cells and 10 to 15 epithelial

cells per high power field; with an occasional granular cast. Stool: 1+ benzidine. Cardiolipin test: negative. Blood chemistry: non-protein nitrogen, 34 mg. per cent; sugar, 275 mg. per cent; total protein, 5.3 gm. per cent; albumin, 2.7 gm. per cent; globulin, 2.6 gm. per cent; alkaline phosphatase, 4.2 Bodansky units; cephalin-cholesterol flocculation, 2+; thymol turbidity, 1 unit; total bilirubin, less than 0.8 gm. per cent. L.E. cell test: negative. Agglutinations: cold agglutinins, negative; thyroid, 1+ at 1-160; paratyphoid, 2+ at 1-150; brucella, negative. Throat culture: heavy growth of alpha streptococci, few neisseriae, few colonies of Staphylococcus aureus, few yeast colonies. Stool culture: no pathogens. Blood cultures (five): negative. Urine cultures (two): Staphylococcus albus. First strength PPD test: negative. Roentgenogram of the chest: cardiac enlargement, moderate; left ventricular enlargement, bilateral minimal pleural effusion. Electrocardiogram: abnormal form of ventricular complex, suggestive of left ventricular strain; ventricular premature contractions.

Immediately after admission a lumbar puncture was performed. The initial pressure was 150 mm. of water; after removal of 8 ml. of clear fluid the final pressure was 100 mm. The fluid contained five cells and 76 mg. per cent of protein; the sugar was 159 mg. per cent, the colloidal gold curve flat, the Wassermann negative and the cultures sterile. The patient was at first moderately confused and lethargic, but was able to sit up and converse. Her conjunctivitis cleared rapidly with local treatment. Anorexia persisted, however, and it became necessary to give her intravenous fluids. On the fifth hospital day, because of persistent abdominal distention, an obstruction series was obtained and interpreted as showing paralytic ileus. Two opacities noted in the right upper quadrant were thought to represent gallstones. On the following day intravenous pyelograms were made and read as interminate. On these films, however, the two opacities previously described were again seen and, in addition, a similar opacity was present in the left upper quadrant. Four days later the latter opacity could not be identified on retrograde pyelograms. On the sixth hospital day a bone marrow aspiration was performed. The marrow was described as hyperplastic, showing considerable stimulation and hyperplasia of the granulocytic cells, but no diagnosis was established. Culture and guinea pig inoculation of this material were negative for acid-fast organisms and for fungi. On this same hospital day the red blood cell count was 2.5 million and the hemoglobin 8.7 gm. per cent. On the seventh hospital day antibiotic treatment in the form of 500,000 units of penicillin intramuscularly every four hours and streptomycin, 0.5 gm. intramuscularly, twice daily, was begun. On the tenth hospital day a complete genitourinary work-up was performed including retrograde pyelography. The impression obtained from these procedures was that the patient had granular urethritis and cystitis. A paracentesis was performed on the eleventh hospital day because it was believed the patient had free fluid in the abdomen, but only 10 ml. of yellow fluid which clotted immediately were obtained. Cultures, including those for acid-fast organisms, were negative. Protein concentration of this fluid was 3.7 gm. per cent. The patient was then given two blood transfusions and her hematocrit rose to 36. Several stools were negative for occult blood. On the twelfth hospital day when her non-protein nitrogen had risen to 41 mg. per cent, a pericardial friction rub was heard. On this same day a consultant saw the patient and noted ulcerative stomatitis and glossitis as well as the friction rub. A second electrocardiogram at this time showed no change from the first. On the thirteenth hospital day because of persistent tachypnea, venous pressure and arm-to-tongue circulation time were determined; the former was 250 mm. of saline, the latter thirty seconds. Shortly thereafter the patient had a sudden onset of severe respiratory distress while attempting to use the bedpan. She became cold and clammy and on examination the expiratory phase of respiration was prolonged, but the lungs were clear to auscultation. The blood pressure was 150/100, the pulse 120 and regular. Treatment at this time included digitalization by the intravenous route. Tachycardia persisted but respiratory distress improved. An electrocardiogram obtained four hours after the attack was interpreted unofficially as compatible with pulmonary embolism and right ventricular strain. Twenty-four hours later anticoagulant therapy was begun. On the fourteenth hospital day dullness and tubular breath sounds were noted at the left base. The white blood cell count had risen to 20,000, with 56 per cent segmented neutrophils, 11 per cent non-segmented neutrophils, 26 per cent lymphocytes and 8 per cent monocytes. On the fifteenth day the fever re-

curred, but the pericardial friction rub disappeared. Repeat roentgenogenograms of the chest were interpreted as showing left ventricular enlargement with pulmonary congestion. At this time the non-protein nitrogen was 63 mg. per cent. An electrocardiogram showed an abnormal form of ventricular complex, digitalis effect, low voltage and a semi-horizontal heart position. Meanwhile the stomatitis was clearing with non-specific mouth care. On the seventeenth hospital day, January 23, 1954, the patient had a sudden episode of wheezing and cried out. She perspired profusely, became pulseless and had expired by the time the physician reached her bedside.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: The patient was a seventy-eight year old woman who had had mild diabetes for at least five years. The present illness apparently began about three weeks prior to admission when she developed fatigue and anorexia; two weeks later she became lethargic and had occasional chilly sensations. Five days before her admission her temperature was found to be 102°F. She was treated with oxytetracycline without any effect. Three hours before entry she awakened with pain in the eyes and headache, and, while walking in the bathroom with her eyes closed, fell, striking her head on the bathtub. When seen at the hospital physical examination revealed bilateral conjunctivitis, rales at the lung bases, normal cardiac size and function and a protuberant abdomen. The laboratory data included a mild normocytic, normochromic anemia, a slightly elevated white blood cell count, and hyperglycemia and glycosuria. One stool was weakly positive for occult blood, but one other was negative. The non-protein nitrogen was borderline or slightly elevated. Urine cultures were positive for Staph. albus on two occasions. During the early portion of her hospital course she was febrile, with elevations up to 39°C. At this time frequent descriptions of various degrees of abdominal distention were in the hospital record. I am told by the house officer who took care of the patient that distention persisted, although as time went by less note was taken of it, and despite it there was no nausea, vomiting, abdominal pain or tenderness. The patient remained anorectic. Her mental status varied, but more often than not she was very lethargic, obtunded and confused. On the sixth hospital day the serum sodium was found to be low and was corrected by administration of hypertonic saline solution without any effect on the patient's clinical status. On the eleventh hospital day, because the continuing abdominal distention suggested ascites to some observers, a paracentesis was performed; only 10 ml. of yellow fluid were obtained which clotted immediately. On the following day a pericardial friction rub was heard. At this time the non-protein nitrogen had risen to 41 mg. per cent. The patient was seen by a consultant who called attention to glossitis and stomatitis, and also described a prolonged expiratory phase in her respirations. On the next day, about thirty-six hours after the onset of the pericardial friction rub, while the patient was on the bedpan there was sudden respiratory difficulty and collapse, This episode was not characterized by cough, hemoptysis or chest pain, and there was no immediate change in the blood pressure. While the attack was going on the pressure was found to be 150/100; however, over the course of the next half hour it fell to 120/80 and remained at about 110/70 for the last three days of her illness. On the same night an electrocardiogram was taken. It was read as compatible with pulmonary embolism. On the following day dullness and bronchial breath sounds developed below the angle of the left scapula. These findings were interpreted by some as Ewart's sign. The pericardial friction rub became much less intense and some observers could not hear it at all. The white blood cell count rose to 20,300. On the seventeenth day there was a second attack of respiratory distress, collapse and death. Dr. Elliott, will you discuss the x-rays?

DR. GLADDEN V. ELLIOTT: Unfortunately, as is the case with many ill patients, our examinations were technically not of the best quality. The first examination of the chest taken the day after admission was not remarkable. The heart was thought to be minimally enlarged; a small bilateral pleural effusion obscured the costophrenic angle bilaterally. The left upper lung field was slightly more radiolucent than the right, probably because fewer vascular densities were present on the left. In addition, the films demonstrated calcified nodes, calcification of the aorta and hypertrophic arthritis of the spine. On the fifth hospital day the patient had her first radiographic examination of the abdomen. On the erect film a triangular density behind the cardiac silhouette in the space normally occupied by the left lower lobe was seen. This density, together

with the radiolucency of the left upper lobe, was considered consistent with left lower lobe atelectasis. Two rather widely separated ring-like radio-opacities were also noted in the right upper quadrant. The last film of the chest was obtained sixteen days after hospital admission, shortly after the patient had the acute episode while on the bed pan, and showed increased density bilaterally, compatible with acute pulmonary edema, or so-called azotemic pneumonitis. The radiolucency in the left upper lobe and the bilateral pleural effusion persisted. The lateral view revealed an increase in density posteriorly, due either to pleural effusion, or to atelectasis and pneumonia of the left lower lobe. There had been a definite increase in cardiac size, perhaps representing a pericardial effusion. A pulmonary embolus might have produced the difference in radiolucency in the two films, although it would not have accounted for the density in the left lower lobe.

DR. SCOTT: Such an embolus would have occurred before the first films were taken, would it not?

DR. ELLIOTT: Yes. There was no roentgenologic change following the sudden episode in the hospital. A second area of interest radiologically was the abdomen. I have previously mentioned that two opaque shadows, thought to be gallstones, were seen in the right upper quadrant. There was also a moderate degree of gas throughout the intestinal tract, presumably due to paralytic ileus. On the films made at the time of pyelography two calcifications in the right upper quadrant were again evident, but, in addition, just above the left iliac crest was a third ring-like shadow, similar in appearance to those previously seen in the right upper quadrant. The shadow appeared constantly on all five films exposed during the urographic examination. When retrograde pyelograms were made on the tenth hospital day, the two opaque shadows in the right upper quadrant were still apparent, but in spite of diligent search one could no longer demonstrate the ring-like opacity in the left upper quadrant. The left renal collecting system appeared within normal limits. The infundibulum of the upper pole of the right kidney was not visualized on either the intravenous or retrograde pyelograms, possibly due to the presence of a small tumor in the upper pole of the right kidney. In summary, the increase in heart size and evidence of pulmonary congestion were compatible with pericarditis, which also could have explained the bilateral pleural effusion, although the latter could have resulted from pulmonary infarction. In the abdomen, gallstones were definitely present. A confusing ring-like shadow in the left abdomen seen on the sixth hospital day, but not subsequently, must have been either an artifact or a gallstone that had been passed through the biliary system into the intestinal tract. Finally, there was a filling defect of the upper pole of the right kidney which may or may not have been due to a tumor.

DR. SCOTT: We have a number of problems to solve. First of all, the patient may have had an underlying disease which explained the first part of her illness, and then may have suffered an acute episode, unrelated to the underlying disease, while in the hospital. On the other hand, of course, both phases of the disease may have been due to the same underlying cause. Since the patient was elderly, it is possible that she had a common disease which gave unusual symptoms and signs. There are many leads in the protocol, most of them pointing to various uncommon diseases. In order to facilitate discussion, I have listed some of the diagnoses considered while the patient was alive. A number of these can be easily eliminated, and additional ones may come to mind as we go along. First, infection of the central nervous system; second, primary ocular disease; third, primary pulmonary disease, fourth, the phantom abdominal opacity, as I have called it; fifth, abdominal Hodgkin's disease; sixth, leukemia; seventh, urinary tract infection; eighth, tuberculous peritonitis; ninth, pseudomyxoma peritonei. Dr. Kenamore took care of this lady and I shall ask him to begin the discussion.

DR. BRUCE D. KENAMORE: When this lady was admitted, the house staff and I believed that the signs were primarily those of a central nervous system infection. A lumbar puncture was done promptly, and the negative findings excluded that possibility.

DR. SCOTT: Dr. Reinhard, will you comment on abdominal Hodgkin's disease and leukemia. You will recall that recently another elderly patient discussed in one of these conferences had abdominal Hodgkin's disease.

DR. EDWARD H. REINHARD: Since I examined the bone marrow I believe one can definitely eliminate leukemia; although there is very little to point to abdominal Hodgkin's disease, it is a diagnosis which is difficult to exclude categorically.

DR. SCOTT: Dr. Harford, several infectious diseases come to mind, particularly urinary tract infection.

DR. CARL G. HARFORD: Only four white cells were reported in the urinary sediment. It is true that urinary tract infections in old people may not be associated with marked pyuria, but it is difficult to be impressed with urinary infection as the cause of the patient's illness with so few cells. Similarly, recovery of Staph. albus on only two occasions is not of significance in my opinion.

DR. SCOTT: Would you care to make any comments about tuberculous peritonitis? Its presence may be unassociated with many clinical signs, especially in elderly patients.

DR. HARFORD: If the patient had tuberculosis, it would have to be assumed that it was disseminated. In addition to the lack of clinical evidence, bone marrow inoculated into guinea pigs failed to yield positive results.

DR. SCOTT: Dr. Mendeloff, what do you think about the so-called "phantom opacity?"

DR. ALBERT I. MENDELOFF: If it is assumed that it was a gallstone, and it certainly resembled the other two gallstones more than it resembled anything else, it must be remembered that gallstones passing into the intestinal tract usually get there not through the usual biliary channel but rather by rupturing of the gallbladder or the common duct. Pain, which is ordinarily severe when this event occurs, may be absent in the elderly, but one would expect to find air in the biliary tract on x-ray; since there was no air visible, I would be reluctant to accept the foregoing explanation and can suggest only that the "phantom opacity" was indeed an artifact. The patient may have had low-grade cholecystitis, which could have accounted for her fever.

DR. SCOTT: Presumably those taking care of the patient concurred in your opinion, because not a great deal of attention was paid to the opacity. I personally was impressed by it when I reviewed the films and would be unwilling to rule out a rupture of a gallstone into the intestinal tract.

DR. REINHARD: Many shadows of that sort noted initially and not again are due to a radiopaque pill or tablet of some sort. Is that possibly true here?

DR. ELLIOTT: We have a set of radiographs of standard pills but in this instance the opacity was ring-like, and I doubt that it was a pill.

DR. ROBERT J. GLASER: Before you finish discussing infections, there is one additional comment that might be in order. Since this lady was quite old, she probably had more than one disease, but the consultant's note about glossitis and conjunctivitis suggests the possibility of Stevens-Johnson's disease, which is characterized by ulcers involving the mucous membranes, and, in its more severe form, by pneumonitis. Although no etiologic agent has ever been isolated, in many ways the features of the disease are compatible with a viral etiology. There are also those who believe it to be an allergic reaction to some chemical or bacterial agent.

DR. SCOTT: I meant to include erythema multiforme exudativum, without erythema, in the list I read previously. Dr. Wood, who saw this patient, made the same suggestion. In retrospect, Dr. Wood, do you still believe that Stevens-Johnson's disease is likely?

DR. W. BARRY WOOD, JR.: I had difficulty in reconciling all the features of this case, and after going over the details with Dr. Kenamore and the house staff, the diagnosis of Stevens-Johnson's disease seemed to bring more of the findings together than any other I could suggest. It came to my mind particularly because of the lesions in the patient's mouth—large ulcers which could have been due to a combination of factors including prolonged illness with fever, mouth breathing and poor oral hygiene. On the other hand, initially she had signs of conjunctivitis, which is characteristic of Stevens-Johnson's disease. She also developed the pulmonary lesions that the radiologists described as pneumonitis and, as indicated by Dr. Glaser, pneumonia occurs in severe forms of Stevens-Johnson's disease. Had there been lesions on other mucous membranes we would have been even more inclined to accept the diagnosis.

DR. SCOTT: According to the record, both the conjunctivitis and the stomatisis cleared promptly after the institution of non-specific measures, which speaks against Stevens-Johnson's disease. Is pericarditis a common finding?

DR. WOOD: No, and that fact militated against the diagnosis more than any other point. I was not able to find a single case report in which pericarditis was described in erythema multiforme exudativum.

DR. SCOTT: Dr. Glaser, what other causes for pericarditis should be considered?

DR. GLASER: One of the most common would be myocardial infarction. The patient was elderly and could have suffered an infarction concomitant with the episode of stress on the bed pan. Another possibility would be metastatic

tumor to the pericardium or epicardial surface of the myocardium.

DR. SCOTT: Could she have had uremic pericarditis?

DR. GLASER: The non-protein nitrogen was only slightly elevated; one expects much higher values before pericarditis develops.

DR. SCOTT: Dr. Goldman, the patient had a paracentesis the day before the pericardial rub appeared. Could air in the peritoneal cavity dissect its way into the pericardium or surrounding mediastinum and produce sounds such as were observed here?

DR. ALFRED GOLDMAN: The only time I have seen air get into the mediastinum after pneumoperitoneum was when excessive pressure was employed. The likelihood of that having happened here is small indeed.

DR. SCOTT: Insofar as we know, the amount of air introduced at the time 10 ml. of fluid was drawn was insignificant. Dr. Massie has reviewed the electrocardiograms, and I am going to ask him to comment on them now.

DR. EDWARD MASSIE: The clinical picture here—a seventy-eight year old lady with signs of pericarditis, leukocytosis and collapse while on the bed pan—lacks only chest pain to have been classical for myocardial infarction. The pericarditis lasted only three days; this short duration is entirely in keeping with infarction. The information to be obtained from the electrocardiograms is pertinent. Q waves were present in leads V_1, V_2 and V_3 and a small R wave was seen in V_4. There was no clockwise rotation. Three tracings confirmed these findings and indicate, even without S-T segment elevation or depression, that the patient had an anteroseptal infarction.

DR. SCOTT: Did the changes develop sequentially?

DR. MASSIE: The first electrocardiogram showed only small R waves and the second early Q waves. Because there is little difference between the two tracings, however, one cannot predict from them when the acute episode occurred. The final tracing was read unofficially as compatible with pulmonary embolism, and presumably showed sudden changes including among others an incomplete or a complete right bundle branch block, and striking inversion of T waves in leads V_1, V_2 and V_3; it is true that such changes can appear and disappear within a day, or indeed even hours.

DR. SCOTT: Is it your opinion, Dr. Massie, that the myocardial disease could have explained the entire course of the patient's illness, beginning three weeks before she came to the hospital?

DR. MASSIE: I would hesitate to assume that it began that far back but it is conceivable.

DR. SCOTT: You think it more likely that the first of the 2 attacks of respiratory distress resulted from myocardial infarction?

DR. MASSIE: Yes.

DR. SCOTT: We still are not clear then as to what was going on when the patient first became ill with fever?

DR. HARFORD: It has been noted repeatedly that fever of unknown origin can be due to myocardial infarction, or for that matter to thromboses or infarcts in many organs in the body. If one is looking for an infectious cause, one of the possibilities is salmonellosis but the pericarditis is an uncommon feature of salmonella infections.

DR. SCOTT: Some of the features of the patient's illness made me think of pancreatitis in passing.

DR. WOOD: The presence of gallstones is at least compatible with that diagnosis, although when I saw her in the hospital I did not think of it. I would like to comment on this terminal episode. None of us had a very good idea as to what disease she had originally, but following the bed pan episode, we believed that acute pulmonary infarction or coronary occlusion had occurred. Both are common and both develop under such circumstances; differentiation is often difficult. An electrocardiogram was obtained promptly and was interpreted by Dr. Frank Norbury and others of us as indicative of right ventricular strain. Since right ventricular strain may be seen in pulmonary infarction or posterior myocardial infarction, perhaps Dr. Massie will discuss the differentiation of these two lesions in terms of electrocardiographic findings.

DR. MASSIE: Dr. Norbury described a QR pattern, T wave inversion in V_1 and V_2, and S waves in V_4, V_5 and V_6. He stated in his note, however, that the S waves were not very deep. One would be more certain had they been deeper, but on the basis of Dr. Norbury's description, one would assume that the patient had a pulmonary embolism. One practical consideration comes to mind, namely, the positioning of the precordial electrodes. Unless one is certain about the placement of the electrodes, particularly when tracings are made in an emergency at night, he cannot interpret a given tracing with confidence. This lady may have had a pulmonary infarction but I suspect that all

of her illness was actually due to myocardial infarction.

DR. SCOTT: In conclusion, it appears that no one of us is very certain about the underlying disease in this woman, but we believe that the terminal event was either pulmonary or myocardial infarction.

Clinical Diagnoses: Diabetes mellitus, arteriosclerotic heart disease, ? pulmonary infarction, ? myocardial infarction and cholelithiasis.

PATHOLOGIC DISCUSSION

DR. BARBARA F. ROSENBERG: Both pleural cavities contained clear yellow fluid, 250 ml. in the right and 580 ml. in the left. The upper portions of the lungs were pink and crepitant; the lower portions were firmer and purple. On cut section the surfaces were red and exuded a small amount of frothy pink material. No thrombi were found in the major pulmonary arteries. The liver was congested and the gallbladder was thickened and edematous, with three stones about 1.5 cm. in diameter within its lumen. The kidneys were small, weighing 100 gm. each. They had a finely granular surface over which were scattered somewhat coarser granules. Over one-third of the surface of the right kidney was a depressed pyelonephritic scar with nubbins of more normal renal tissue rising above the base of the scar. There were some petechiae in the pelves of the kidneys. Nothing was found in the peritoneal cavity to explain the "phantom opacity" seen on x-ray.

The heart weighed 330 gm. In the pericardial cavity were 20 ml. of yellow fluid. The surface of the heart was rough, shaggy and red, and almost the entire left ventricular myocardium, except for a small portion of the lateral wall, was streaked with yellow and red. This infarct extended up to the base of the valve and throughout the septum. In the coronary arteries large plaques were found in both the anterior descending and right branches. These plaques almost completely occluded the lumens of both arteries close to their origin. The circumflex branch was relatively free of plaques. In the anterior descending coronary artery there was a reddish brown thrombus over the partially occluding plaque; in the right coronary there was a grey, occluding mass which had the appearance of an organized thrombus.

DR. ROBERT A. MOORE: On the basis of the gross findings this case seems straightforward. We have a patient, seventy-eight years old, with moderate to advanced arteriosclerotic vascular disease, nephrosclerosis which has decreased the size of the kidneys from 150 to 100 gm., a high degree of arteriosclerosis in the coronary arteries and total occlusion of both the right and left descending coronary arteries by thrombi. The greater part of the posterior wall of the left ventricle and all the interventricular septum are the site of an infarct of fairly recent appearance. In the brain there were foci of older encephalomalacia indicative of the effect of the same arteriosclerotic process upon that organ. However, difficulty is encountered when we attempt to correlate these anatomic findings with the clinical history. Grossly, the myocardial lesion is of recent origin, more recent than the twenty-four days of the patient's total illness. In other words, the determination of the chronology of this patient's disease during the last twenty-one to twenty-four days of her life will depend upon the evaluation of the respective ages of the various lesions basically due to or caused by arteriosclerosis.

Figure 1 is from a section of the left descending coronary artery in which the greater part of the lumen has been obliterated by an arteriosclerotic plaque and the lumen itself is occupied by a thrombus, a part of which has broken off during the preparation of the section. This thrombus in the left descending coronary artery showed no evidence of organization so that one might suppose it had been there only a matter of days; the thrombus in the right coronary artery showed very definite evidences of organization and had been present therefore for several weeks. It is difficult to estimate accurately the duration of time that it takes thrombi to organize in arteriosclerotic vessels. A thrombus can organize in a normal vessel much more rapidly than in an arteriosclerotic one where it is surrounded by tissue that has already degenerated. Around the outside of this vessel is an incidental finding, namely, the presence of numerous cholesterol clefts with some cellular infiltration in association with them in the adventitia. I would assume that some time in the past, perhaps months ago, there had been a good deal of hemorrhage into the adventitia of this vessel and that this finding represents the end result.

Let us turn next to the infarct. We have studied a number of sections of the heart from different areas in order that we might see whether or not any parts of the infarct vary in age. Every section shows infarcted tissue of the same appearance. The apparent age of all parts of this lesion is relatively short because, as is

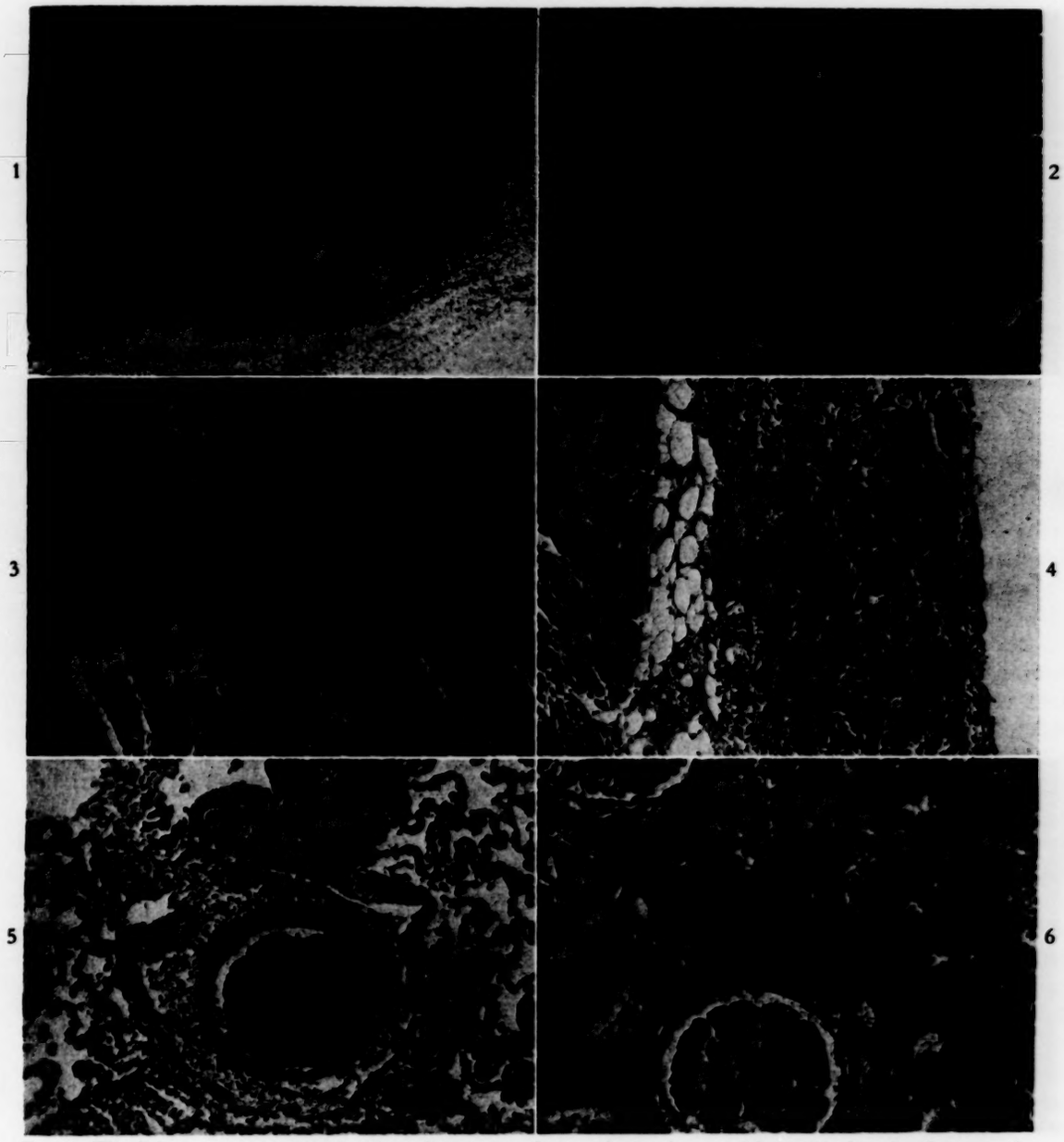

FIG. 1. The left coronary artery showing almost complete occlusion by an old arteriosclerotic plaque and a recent thrombus within the pre-existing lumen. The adventitia contains many cholesterol clefts probably indicative of old perivascular hemorrhage.

FIG. 2. The myocardium showing extensive hemorrhage into the semi-necrotic tissue without disruption of architecture or evidence of reaction by the tissue. The erythrocytes are well preserved.

FIG. 3. The myocardium showing extensive interstitial fibrosis indicative of long-standing coronary insufficiency.

FIG. 4. The pericardium showing an extensive organizing fibrinous pericarditis apparently over a week's duration. There is no evidence of infectious etiology in this lesion.

FIG. 5. A section of a small artery in the lung showing one of the organized thrombi that were present in many of these small vessels.

FIG. 6. The kidney showing thickening of arteriolar walls and interstitial fibrosis and cellular infiltration indicative of a considerable arteriolar nephrosclerosis.

FIG. 7. Early necrosis in the wall of an afferent arteriole in the kidney. This finding is compatible with the indications of a rising serum non-protein nitrogen in combination with the pre-existing arteriolar nephrosclerosis.

shown in Figure 2, the red blood cells which have been poured out into semi-necrotic tissue are still well preserved and have not undergone degeneration. This infarct corresponds very well with the events of about the eleventh day of hospitalization with death on the 17th day; it could well be a six-, seven- or eight-day old infarct, but I doubt that it could be three weeks old. There is absolutely no reaction or proliferation of cells of any sort in the surrounding tissue. On the other hand, this patient has been suffering for a long period of time from coronary insufficiency, because sections such as Figure 3, from outside the infarct, show scattered masses of loose fibrous tissue throughout the myocardium. There is, unfortunately, no lesion of a stage between these two, one of which represents long continuing or healed coronary insufficiency and the other a very fresh infarct. Figure 4 illustrates another puzzling feature. The greater part of this photomicrograph shows a mass of fibrin on the pericardial surface; but where the fibrin is in contact with the epicardium, there is active proliferation of fibroblasts and capillary vessels. This process represents organizing pericarditis and is older, I believe, than one week. There is, therefore, pericarditis of one age and a myocardial infarct of another in the same heart, the former antedating the latter.

Sections of the lung showed a number of thrombi of varying ages in the pulmonary arteries. In Figure 5 there is seen one such thrombus, completely covered by endothelium and invaded by fibroblasts. Thrombi in other small arteries are of quite recent appearance. They indicate that the patient had either multiple primary pulmonary thrombi or multiple small pulmonary emboli over an extended period of time, consistent with her three weeks' illness. A few small foci of what appeared to be relatively bland interstitial pneumonitis were also in the lungs. In Figure 6 the degree of arteriosclerosis observed in the kidneys is demonstrated. It was responsible for the reduction of the weight of the kidneys, quite aside from the large pyelonephritic scar in the right kidney that accounted for the distortion of the renal pelvis. In the kidney there was also the very interesting lesion shown in Figure 7, namely, necrosis occurring in the wall of an afferent arteriole of a glomerulus. There were a few other arterioles throughout the body that show similar very early necrosis. Their presence leads one to conclude that the patient was about to go into a malignant phase of nephrosclerosis. Although the patient had diabetes, there were no lesions in the glomeruli that we associate occasionally with diabetes. In the pancreas there were a few hyalinized islets but no other findings of note.

In summary, there is good evidence that this patient had a coronary occlusion and myocardial infarct about a week before death, and that for a considerably longer period of time she had had coronary insufficiency. Partially organized pericarditis apparently antedated the infarct and seems to correspond more closely with the total duration of the final illness. Its pathogenesis is obscure; there is certainly no evidence it was of infectious origin. Over a period of several weeks she had also multiple small thrombi or emboli in her pulmonary arterial system. There was considerable arteriolar nephrosclerosis with evidence of terminal renal failure in the form of early necrosis of arteriolar walls. No changes in any other organs were found to explain the chronologic relationships between these events or to contribute significantly to the terminal illness.

Final Anatomic Diagnosis: Arteriosclerosis, generalized, especially of the coronary arteries; recent and organized thrombi in the coronary arteries; recent infarct of the septum and left ventricle of the heart; organizing pericarditis; thrombi in small pulmonary arteries; arteriolar nephrosclerosis, moderate, with early necrosis of arterioles.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Spontaneous Rupture of the Esophagus

With a Note on Tissue Necrosis from Nor-epinephrine

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SPONTANEOUS rupture of the esophagus is a disaster which until recently carried a mortality rate approaching 100 per cent. Since the first case by Barrett[1] in 1947, twenty-one cases[2–5*] have been reported in the literature as recovering following surgical therapy. As recovery depends not only on adequate surgical therapy but also on early diagnosis, and as the majority of reports have appeared in the surgical literature,[2–12] it seemed advisable to report our two cases, one with recovery.

Diagnosis in the majority of cases can be made with relative ease provided one has previous knowledge of the disease. In this paper, as in other reports, spontaneous rupture of the esophagus is defined as rupture with no pre-existing disease or traumatic lesion of the esophagus.

The clinical findings in the majority of cases are quite typical. The symptoms begin when a previously well, middle-aged male vomits severely usually following an alcoholic debauch or unusually heavy meal. This is immediately followed by severe upper abdominal and lower substernal pain radiating into the back. Vomiting always precedes the pain and usually contains incompletely digested food and frequently streaks of blood, more often bright red than coffee ground in appearance. The pain is extremely severe, quite steady in character, boring in nature and unrelieved by opiates. Even at the onset the patient is well aware that he is critically ill.

On physical examination the patient appears mortally ill, is quite restless, apprehensive and unable to cooperate well. Shallow, rapid respirations are present and cyanosis may be noted. Examination of the abdomen reveals varying degrees of abdominal rigidity, frequently of such severity that abdominal operations have been undertaken. It is usually difficult to examine the chest adequately but at the onset the findings are frequently normal. As the disease progresses signs of hydro- or pneumothorax become evident and subcutaneous emphysema may appear in the neck. This latter finding, however, is variable in occurrence, time of onset and degree. It is, when present, an extremely important and helpful diagnostic clue. Severe progressive shock ordinarily occurs several hours after the onset of the disease.

X-ray examinations are most important in the diagnosis as over 90 per cent of plain postero-anterior films of the chest will be abnormal, and lateral films will increase this percentage slightly. Chest films in many cases (66 per cent) reveal evidence of mediastinitis with mediastinal and neck emphysema. Hydro- or hydropneumothorax may be present at the onset or commonly appear later (91 per cent). In no case has air been noted under the diaphragm.[2] An esophagram, preferably using iodized oil, is diagnostic if the radiopaque material is seen extending from the esophagus into the mediastinum.

In the differential diagnosis of this condition several diseases may occasionally be confusing. However, if the typical clinical picture is present the diagnosis is so clear-cut that, as has already been reported in the literature[6] and as is true in both of our cases, the diagnosis may be made over the telephone. Coronary occlusion and dissecting aneurysm of the aorta may be confusing but these, after careful study, can usually be excluded. Spontaneous mediastinal emphysema may give similar x-ray findings but can usually be differentiated by history and other studies. Spontaneous pneumothorax or pneumo-

* In the discussion of Dr. Anderson's paper other cases were reported but the etiology and total number is not clear.

hemothorax, as well as pulmonary embolism, should give no great difficulty. Pancreatitis with pain radiating to the back, as well as other abdominal crises, may offer temporary early confusion. The most frequently misdiagnosed condition appears to be perforated peptic ulcer and, as has already been noted, abdominal exploration has been carried out on frequent occasions, as was true in one of our cases. X-ray examination of the chest as well as the history of vomiting prior to onset of pain should be all that is necessary to make a tentative diagnosis.

The pathologic lesion in this condition is quite constant, rupture occurring most commonly on the left posterolateral aspect of the esophagus just above the diaphragm. It rarely may be on the right and very rarely at a higher level. There is one slit which is always longitudinal in direction and has a sharp clean edge as though cut with a knife, but may vary greatly in size from pinpoint up to 8 cm. in length. As has been previously mentioned no evidence of antecedent disease of the esophagus is present. Purulent mediastinitis rapidly appears and pleural effusion, usually on the left, is soon evident. Pneumothorax does not occur unless rupture of the mediastinal pleura takes place.

The mediastinitis is of such severity that the majority of cases (85 per cent) expire within forty-eight hours unless early definitive surgery is carried out, most of these deaths occurring within twenty-four hours.[6] A few cases form localized abscesses in the mediastinum and survive for longer intervals. There appears to be no sure method of differentiating this latter group early in the course of the disease.

The cause of the rupture in most cases is a sudden increase in pressure within the esophagus.[6] It has been postulated that this is brought about by concomitant pylorospasm and spasm of the cricopharyngeus muscles during a period of extreme vomiting.[1,12] The bursting pressure of the human esophagus has been investigated in cadavers and found to be approximately 2 to 6 pounds per square inch; however, sudden increases of pressure appear to be more likely to tear the esophagus than gradual distention.[6] The interesting relationship of brain insults[13,14] to perforation is still inadequately understood. Esophagomalacia[12] is believed by some to be the primary factor. A more logical cause would appear to us to be altered nervous control of muscles during retching and vomiting, allowing great pressure to develop within the esophagus. The reasons for the consistent rupture in the lower left esophageal wall again are not completely known and many theories have been advanced.[6] These include angulation of the esophagus in this area, thinning of the muscle and entrance of vessels and nerves into this portion. In addition, the lower esophagus has less external support than the remainder. Experimental work in cadavers has shown that almost all ruptures thus produced occurred at this site.

Ideally, treatment should begin with early diagnosis. Immediate thoracotomy is indicated in spite of the patient's extremely critical appearance. Generally a left transpleural approach direct to the lower esophagus with evacuation of pleural and mediastinal fluid and closure of the rupture is the procedure of choice. We believe that it is important to establish wide drainage of both the mediastinum and pleural cavity. Prior to operation a Levin tube should be passed carefully into the stomach. If the tube passes out through the rupture it can be directed into the stomach at the time of operation. For the first twenty-four or forty-eight hours postoperatively gastric suction is advisable following which time feeding may be begun through the tube. In most cases nutrition can be handled easily in this fashion although in the occasional case jejunostomy may be necessary. Massive antibiotic therapy is in order and general supportive measures to combat shock, toxemia and dehydration will probably be necessary in preparation for, during and after surgery. Nor-epinephrine may be of particular value should the shock not respond to blood or other fluids. Although this drug may be life-saving, its tissue necrotizing effect along the course of the vein of entry requires caution and careful observation in its prolonged use.[15–17]

CASE REPORTS

CASE 1. J. A. R., a fifty-five year old, white, married, male was traveling to South Carolina by train and awoke somewhat earlier than usual on the morning of the onset of his illness. Along with and following breakfast he consumed approximately six to eight cups of coffee to which he was not accustomed, and after leaving the train developed headache for which he took two "headache pills." Thereafter vomiting began, rapidly increasing in severity and of such degree that streaks of bright red blood were noticed by the patient. Within a period of five minutes he

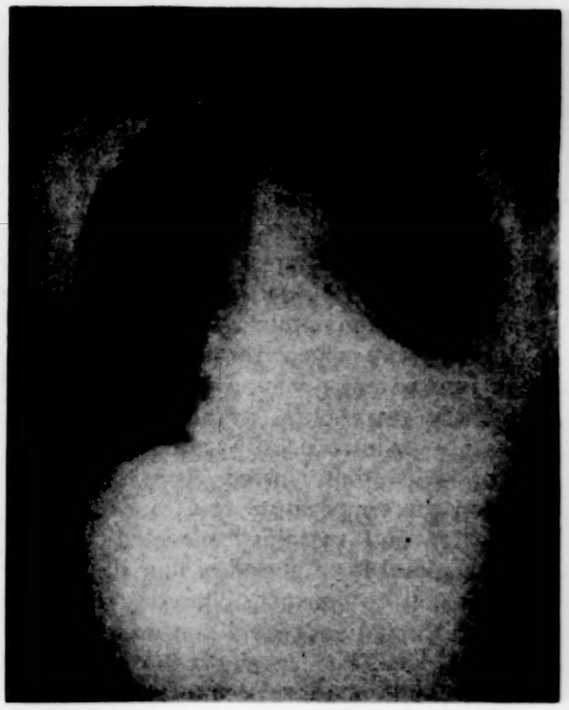

FIG. 1. Case 1. Postero-anterior film of chest showing fluid in the left pleural space, mediastinal and subcutaneous emphysema, and mediastinal widening (four hours postrupture).

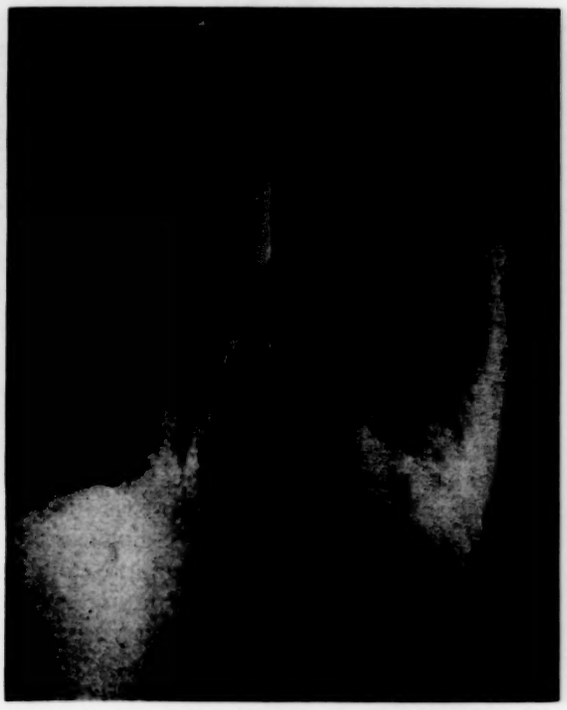

FIG. 2. Case 1. Esophagram, using lipiodol, revealing extravasation into the lower mediastinum and retrocardiac mediastinal air.

developed excruciating pain in the back and marked dyspnea. He stated later that he knew that he was critically ill from the onset.

The patient's past history, family history and marital history were all entirely non-contributory and he had been examined during the previous week by his personal physician in Philadelphia who pronounced him to be in excellent health except for microscopic hematuria. No electrocardiogram had ever been made nor had any investigation of the hematuria been carried out. He had never had any gastrointestinal symptoms whatsoever.

Within five minutes a physician was obtained who recognized the gravity of the situation and gave him morphine sulfate, gr. ¼, and immediately referred him to Columbia for more definitive care with a diagnosis of questionable ruptured peptic ulcer or coronary occlusion. The patient arrived at the Columbia Hospital on October 29, 1952, approximately two hours later having received in the interim a second dose of morphine sulfate, with only minimal relief of pain.

Physical examination at that time revealed an extremely ill patient who was in exquisite pain, quite flushed and dyspneic with short grunting respirations. Cyanosis was not present at that time but appeared later. Blood pressure was 140/90 in both arms, the veins were engorged and both carotid pulses were strong and easily palpable. No subcutaneous emphysema was noted at this time. Examination of the lungs was extremely difficult but no definite abnormalities were noted. The patient could take only short respirations and examination was not entirely satisfactory. The heart was not enlarged and the sounds were of fairly strong intensity and of good quality. No friction rub or murmurs were noted. Examination of the abdomen exhibited extreme rigidity most marked in the upper half without pain to palpation. Both femoral pulses were strong and easily felt. No other abnormalities were noted.

An electrocardiogram showed evidence of left bundle branch block without other significant abnormalities. X-ray examination of his chest (Fig. 1) showed evidence of mediastinitis and questionable widening of the aorta. Subcutaneous emphysema was noted on this film and was now clearly evident on physical examination approximately two hours after the initial examination.

At this time thoracic surgical consultation (G. H. B.) was sought, the diagnosis of ruptured

esophagus made, and this impression substantiated by x-ray studies of the esophagus with lipiodol.® (Fig. 2.) Other laboratory work was unrevealing, hemoglobin being 80 per cent with 4,150,000 red blood cells and 6,900 white blood cells with 87 per cent polymorphonuclears, 10 per cent lymphocytes and 3 per cent eosinophils. Urine examination showed only a rare red blood cell, later specimens showing occasional blood cells and traces of albumin. Serum amylase was 266 units (Somogyi).

Throughout this period of preoperative work-up his condition rapidly deteriorated. Temperature on admission was 96.6°F. and rose to 99°F.; blood pressure rapidly fell to shock levels and cyanosis appeared. The patient was cross-matched and suitable transfusions were begun. Penicillin and streptomycin were given and he was taken to the operating room approximately eight hours after the onset of the rupture. At this time a definite loud mill-wheel type pericardiopleural friction rub was first audible. A Levin tube was passed, the patient was given small amounts of quinidine gluconate intramuscularly and nor-epinephrine (levophed®) was begun prior to surgery. The patient was considered to be in critical condition at this time but surgery was believed indicated in spite of the gravity of the situation.

The operation was carried out under endotracheal anesthesia with the patient on his right side. The left ninth rib was subperiosteally resected and the pleural cavity entered. A moderately large quantity of greyish-brown foul pleural fluid was present. The mediastinal pleura was intact but there was bulging of the lower portion to approximately the size of a grapefruit. This was incised and a large collection of black foul fluid under pressure was evacuated. In addition there was considerable air throughout the mediastinum. There was then found a longitudinal tear in the esophagus just above the diaphragm on the left lateral wall. This straight slit was approximately 1½ inches in length. The mediastinum was foul, all tissues being discolored black. The Levin tube was found to be coiled in the esophagus above the tear. This was threaded into the stomach following which the esophagus was closed with fine silk sutures. The mediastinal pleura was left open and drains were inserted into the mediastinum and pleural cavity. One gm. of streptomycin and 500,000 units of penicillin were placed in the pleural cavity. The lung was inflated and the wound closed. During operation systolic blood pressure was maintained at approximately 90 mm. Hg by infusion of 500 cc. of blood and almost constant nor-epinephrine (levophed).

Almost immediately following operation the patient began to improve, appeared to be much quieter and in considerably less pain. For a period of three days intermittent nor-epinephrine, in addition to blood and constant fluids, was necessary to maintain a systolic pressure of 90. These were given through polyethylene tubing into an ankle vein. Penicillin, 1 million units every two hours, terramycin, 500 mg. every six hours intravenously, and streptomycin, ½ gm. twice daily, were given. Following operation the temperature rose to a maximum of 100.4°F. and remained elevated but not above this level for a period of four days, after, which it fell to normal. The day following operation the patient's condition was obviously much improved. The legs showed no abnormalities. The mill-wheel type murmur was still clearly audible. Gastric suction was discontinued at this time. On the second postoperative day he continued to improve and the pericardial friction rub was last heard on this day. Tenderness along the course of the vein where the catheter was in place was noted for the first time. The significance of this tenderness was not recognized and was erroneously attributed to irritation from terramycin, and ice bags were applied. On the following day the tubing was removed from the vein and terramycin (250 mg. every two hours) was inserted through the Levin tube. Later vitamins, milk, lipomul® and somagen® were added as tube feeding.

Postoperatively empyema developed, fed by a small esophagopleural fistula. Spontaneous healing took place after drainage of the empyema. On the eighth postoperative day the massive antibiotic therapy was gradually decreased and finally discontinued altogether on the forty-eighth postoperative day.

One of the greatest difficulties encountered following operation was the presence of a large slough near the ankle where nor-epinephrine had been given through polyethylene tubing. The first abnormality noted was tenderness, shortly followed by a sharply demarcated area of dusky, dark red discoloration appearing by the third postoperative day. The process gradually increased in intensity even after the tube was removed, and later a large, single hemorrhagic

bulla covered the entire area. This major area was located midway up the medial side of the calf, measuring approximately 4 by 2 inches. The center of this area was at approximately the tip of the indwelling tubing, and a similar smaller area was present at the entrance point. This was followed by complete necrosis of the skin and subcutaneous tissue. Débridement was required and eventual complete closure by suture was carried out three months postoperatively.

Subsequent examination has revealed the patient to be entirely well and asymptomatic. The leg wound and empyema have completely healed. There is no dysphagia and x-ray examination of the esophagus shows no evidence of any lesion. Examination of the urinary tract including intravenous pyelograms but not including cystoscopy never revealed the cause of the microscopic hematuria but this subsequently cleared spontaneously. Left bundle branch block by electrocardiogram persisted. Repeated questioning never revealed symptoms of coronary artery disease.

Case II. J. B. was a sixty-six year old colored male farmer who was well until several days prior to admission on September 11, 1953, to the Columbia Hospital when he developed a simple upper respiratory infection. For this he treated himself with "black draught" and subsequently had a black bowel movement. (This medication routinely causes black stools but this history of self-medication was not obtained until later.) On the morning of admission he felt improved and for the first time in several days ate a large lunch. Originally, the history obtained indicated that the patient suddenly developed severe, excruciating abdominal pain followed by vomiting which contained moderate amounts of bright red blood. He was seen shortly thereafter by a physician who found him to be critically ill and referred him to a very competent general surgeon in Columbia. On arrival in the emergency room approximately two hours later he was extremely ill, doubled up with pain in spite of ½ gr. morphine, slightly dyspneic and in severe shock. The abdomen was "board-like" in nature. Immediate abdominal exploration was believed indicated and he was transferred directly to the operating room. At laparotomy extensive exploration including gastrotomy did not reveal the cause of the patient's symptoms. One of us (C. W. I.) was asked to see the patient eighteen hours postoperatively at which time he was comatose, severely cyanotic in spite of oxygen and tachypneic. The blood pressure was obtainable in spite of his having received 1,500 cc. of blood since admission. The neck veins were markedly engorged but no subcutaneous emphysema was detected. Examination of the lungs revealed rales and wheezing bilaterally but no evidence of hydro- or pneumothorax. The heart sounds could not be distinctly heard and the pulse was 110. The carotid and femoral pulses were present, very weak and equal, and there was no edema. The electrocardiogram obtained a few hours previously was suggestive of posterior myocardial infarction with small Q waves in leads II, III and AVF, minimal elevation of the S-T segments in these leads and reciprocal depression in leads I and AVL.

Immediate x-ray of the chest was obtained with great difficulty and revealed "some increase in density of the entire left lung field as compared with the right. There is a radiolucent shadow along the mediastinum on the left which can be seen through the cardiac shadow." (Fig. 3.) After an unintentional bronchogram was obtained, the Levin tube was finally accurately placed in the esophagus. Esophagram was then obtained showing rapid free flow of lipiodol into the left hemithorax, thus proving the diagnosis of ruptured esophagus. (Fig. 4.) Thoracic surgical consultation was therefore immediately obtained.

It was our belief that the only hope for survival was thoracotomy in spite of profound and protracted shock. After intravenous nor-epinephrine was started and the blood pressure had risen to approximately 100 mm. Hg systolic, light anesthesia was induced with nitrous oxide and oxygen followed by endotracheal ether and oxygen. Cyanosis persisted. Blood pressure, pulse and respiration at this point ceased. The rate of flow of intravenous nor-epinephrine was increased and artificial respiration was carried on by the anesthesiologist. In a few moments the patients condition improved and the operation was begun twenty-eight hours post-rupture. The left pleural cavity was entered posteriorly and a moderate quantity of dirty brown pleural fluid was found. The mediastinal pleura posteriorly was bulging but had not ruptured. This was incised and a large quantity of extremely foul brown fluid containing food particles was evacuated from the mediastinum. No free air was apparent. The mediastinal structures including the pleura

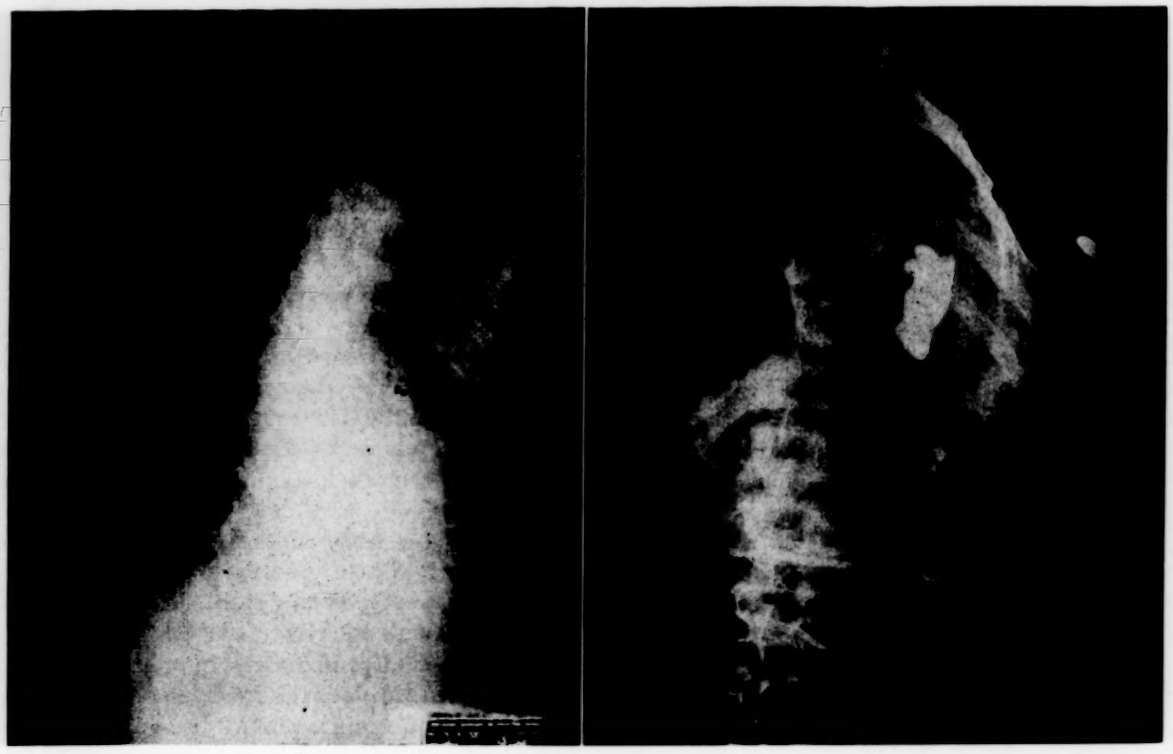

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FIG. 3. Case II. X-ray of chest taken with patient in shock showing haziness of entire left lung field (twenty-six hours postrupture). A small amount of mediastinal air could be detected on the original film but cannot be clearly seen in this figure.

FIG. 4. Same case. Esophagram showing large amount of lipiodol pooled in the mediastinum. The unintentional bronchogram is evident as are the radiopaque dressings on the abdominal wound. The bullet is ancient in origin and unrelated to the present illness.

showed evidence of marked digestion. Immediately following the incision and decompression of the mediastinum the patient's condition began to improve, cyanosis cleared with remarkable rapidity and the strength of cardiac contractions improved strikingly. A single longitudinal slit about 2 inches in length was found in the left posterolateral aspect of the esophagus just above the diaphragm. The previously passed Levin tube was then directed into the stomach, following which the esophagus was repaired with silk sutures. Drains were placed in the mediastinum and pleural cavity, penicillin and streptomycin inserted locally and the wound was closed. Massive antibiotic therapy was begun but in spite of continuous intravenous norepinephrine, anuria became evident, shock and coma persisted and the patient expired twenty-four hours after thorocotomy. It was our impression that death was primarily due to irreversible shock. Even more striking than in Case I, marked tissue necrosis appeared when norepinephrine was being given through an ankle vein, but none was evident when the site of administration was transferred to an antecubital vein. These changes took place in spite of the application of local heat.

Following surgery further history was obtained from the wife who was not originally available for questioning. She indicated to us that the final episode began after the first large meal the patient had eaten in several days. Within one-half hour he began to retch severely, later followed by vomiting and finally by pain.

COMMENTS

These two cases graphically illustrate the importance of early diagnosis and surgical treatment when rupture of the esophagus has occurred. The first case was diagnosed early and surgery was started within eight hours. The second patient did not come to definitive esophageal surgery for twenty-eight hours after the rupture and was moribund at that time. As previous reports have shown that the majority of deaths occur within twenty-four hours,[6] the

time element is of vital importance. We believe that this diagnosis can be made with relative ease if the condition is suspected and certain simple important clues sought. The triad of diagnostic points we wish to emphasize are: vomiting prior to pain, subcutaneous emphysema and abnormal chest x-ray films. It is particularly important to search for these in the "typical ruptured peptic ulcer," and we believe that a routine upright x-ray of the chest should be obtained in all of these cases. The "severe ruptured ulcer" in shock or extremis in which x-ray and laboratory aid is believed unnecessary or too time-consuming is the very case in which these procedures may be life-saving.

The striking improvement in the condition of both of these patients immediately after release of the mediastinal pressure has convinced us of the necessity of prompt surgery. The chances for survival in spite of an obviously extremely critical condition would appear to be improved by such definitive measures. Simple drainage of the pleural space, without release and evacuation of the mediastinal contents, would not have aided either of our two patients as the mediastinal pleura was intact in both and improvement did not occur until the mediastinum was opened.

At the time of our first case we did not realize that nor-epinephrine administered through an ankle vein might cause tissue necrosis.[17–19] Although particular care to avoid this complication was taken in the second case, blanching of the skin at the site of venipuncture occurred almost immediately and was promptly followed by obvious tissue necrosis. This did not occur when the site of administration was transferred to the antecubital vein.[16] Hot compresses have been suggested[16] to counteract the intense vasospasm but were of little value in our second case.

SUMMARY

1. Two cases of spontaneous rupture of the esophagus, one with recovery, are reported.

2. The diagnosis and necessity of early surgery are discussed.

3. The diagnostic triad of vomiting prior to pain, subcutaneous emphysema and characteristic chest x-ray films is emphasized.

4. Attention is called to the tissue necrotizing effects of nor-epinephrine (levophed) when administered through an ankle vein.

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The Taussig-Bing Syndrome*

A Report of Two Further Cases, One Complicated by Aortic Coarctation

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TAUSSIG and Bing[1] in 1949 described a new entity consisting in the aorta rising entirely from the right ventricle, with the pulmonary artery taking origin from the left chamber while straddling a ventricular septal defect. A similar case had evidently been presented earlier by Pernkopf.[2] At least three of the cases presented by Campbell and Suzman[3] had physiologic features found in the original case of Taussig and Bing[1] in that the oxygen content of the pulmonary artery was higher than that of the aorta. A case diagnosed by angiocardiography was presented by Kreutzer and his associates.[4] More recently, Martin and Lewis[5] described a typical case. Two children suffering from this condition complicated by pulmonary stenosis were described by Van Buchem and his collaborators.[6]

Two further cases are presented. Both were diagnosed by angiocardiography. In one the condition was confirmed by autopsy. An unusual association in this case was aortic coarctation which gave rise to a striking appearance during life.

CASE REPORTS

CASE 1. This four month old mongolian female was noted to have a cyanotic right hand soon after birth. Apart from this she seemed to progress fairly well until the age of two months when a cough developed; during the paroxysms cyanosis of the lips and face was seen. This blueness steadily became more constant and widespread.

On admission she was small for her age, with a typical mongolian facies. There was some cyanosis of the brow, cheeks and lips at rest. The right arm was dark blue, in striking contrast to the left arm. (Fig. 1.) The left radial pulse was impalpable, and the femoral pulsations though present were of poor quality. The heart was enlarged. A thrill was felt at the mid-left sternal border; a corresponding systolic murmur (grade 3–4) was transmitted to the axillas and back.

There was no polycythemia. An electrocardiogram showed right axis deviation without definite evidence of a "strain" pattern.

At fluoroscopy (Fig. 2) the heart was enlarged, the pulmonary artery and right ventricle being particularly affected, although there was evidence of some left ventricular enlargement in the left oblique position. The lung fields were hypervascular.

The angiocardiogram (Figs. 3 and 4) showed a transposition of the aorta with levoposition of the pulmonary artery. The failure of filling of the descending aorta gave support to the clinical consideration of a coarctation.

Death occurred at six months following a severe respiratory infection. The autopsy report revealed the following: the aorta, which gave off a normal coronary circulation, rose completely from the right ventricle. (Fig. 5.) An innominate artery divided into the right subclavian and right common carotid. There was an almost complete coarctation between the left common carotid and the left subclavian artery. (Fig. 6.) A patent ductus arteriosus entered just distal to the constriction. The pulmonary artery rose from the left ventricle and straddled a high ventricular septal defect. The atrial septum was intact. The left atrium received the pulmonary veins in a normal fashion.

Comment. This is a typical case of the Taussig-Bing syndrome, although the association of an aortic coarctation appears to be unique. Its presence could be inferred during life from the

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FIG. 1. Case 1. Note cyanosis of right arm and hand as compared to the left.

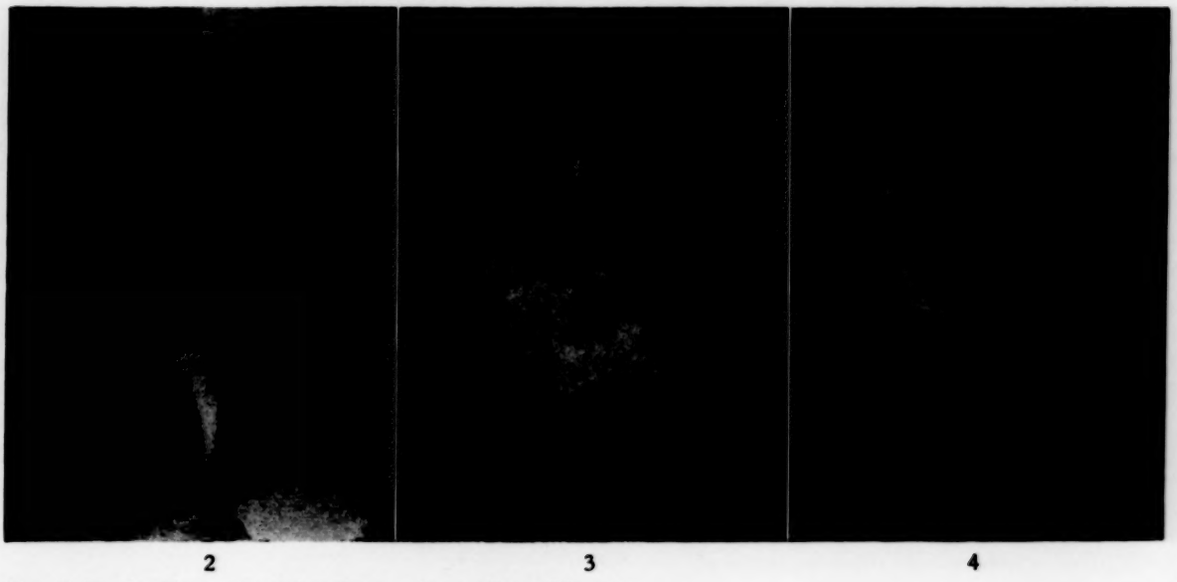

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FIG. 2. Case 1. Postero-anterior view to show enlarged heart.

FIG. 3. Case 1. Angiocardiogram, postero-anterior view. The aorta is seen rising from the right ventricle and giving off the coronary circulation. Note that there is no filling beyond the left common carotid. Medium is seen crossing a ventricular septal defect.

FIG. 4. Case 1. Angiocardiogram, oblique view. The aorta is seen from the right ventricle. The pulmonary artery is in close relationship to the ventricular septal defect.

5 6

FIG. 5. Case I. The aorta is seen rising from the right ventricle. The probe through the ventricular septal defect enters the pulmonary artery.

FIG. 6. Case I. The aorta is opened to show the site of coarctation.

remarkable combination of a deeply cyanotic *right* arm and hand, with an absent *left* radial and brachial pulsation. The course of the circulation was partly confirmed by the angiocardiogram. It would appear that essentially

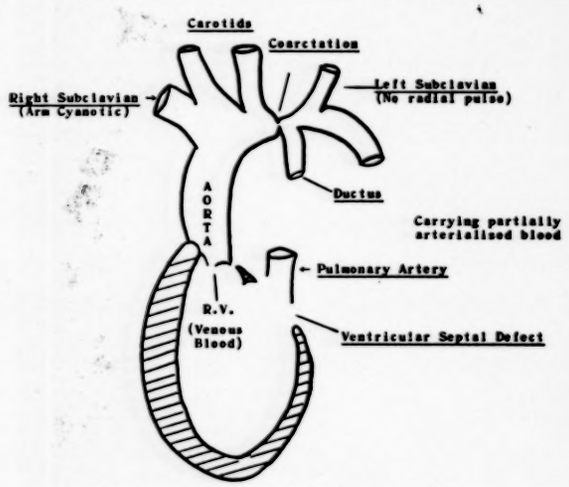

FIG. 7. Diagram of circulation in Case I.

venous blood entered the aorta from the right ventricle to be distributed to the right arm, head and neck. The ductus, carrying pulmonary arterial blood of increased oxygen content (Bing and Taussig 1949, Martin and Lewis

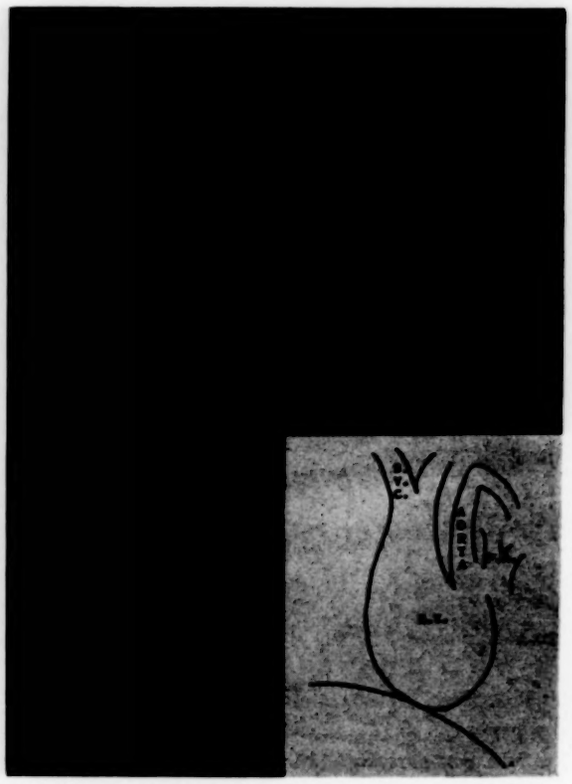

FIG. 8. Case II. The aorta rises from the right ventricle. The pulmonary artery rises internal to this in relation to the ventricular septal defect, as shown in the diagram.

1953), entered the aorta distal to the constriction and was distributed to the left arm and lower limbs. The left arm was thus less cyanotic than the right. Figure 7 summarizes the findings by diagram.

CASE II. This child was seen at the age of three years with a history of frequent respiratory infections. Cyanosis associated with bronchitis had been seen at one year of age, but she had been relatively well until two years later when bouts of cyanosis and respiratory infection became more prominent.

Examination revealed a child of height 82.5 cm. and weight 11 kg. There was slight cyanosis of the lips and face at rest. This increased and became more generalized on exertion. The fingers and toes showed moderate clubbing. The pulses were normal. A systolic thrill and corresponding murmur were present at the mid-left sternal border. The latter was widely transmitted over the precordium and to both axillas. A loud third heart sound was heard. Moderate polycythemia (16.0 gm. hemoglobin) was present. An electrocardiogram showed right axis deviation.

Fluoroscopy and chest films showed moderate cardiac enlargement and convexity of the pulmonary arc. There was some right ventricular enlargement. The lung fields were hypervascular. An angiocardiogram (Fig. 8) showed that the aorta arose entirely from the right ventricle and the pulmonary artery from the left, while overriding a septal defect. The child was subjected to cardiac catheterization, the aorta being readily entered. The pulmonary artery could not be explored.

OBSERVATIONS

Taussig and Bing (1949)[1] in describing this syndrome suggested that the cyanosis and clubbing existed from an early age and was accompanied by a systolic thrill and murmur. Fluoroscopy in their case showed fullness of the pulmonary conus and plethoric lung fields. Physiologically, the condition was characterized by a higher oxygen content in the pulmonary artery than in the systemic circulation. Exercise caused a decrease in the oxygen consumption per litre of ventilation. The children reported by Van Buchem and his associates showed a different fluoroscopic appearance because of the associated pulmonary stenosis. In their cases the pulmonary arc was concave and the lungs oligemic, findings which echo those described by Astley and Parsons[7] in great vessel transposition with pulmonary stenosis.

There is some evidence that the Bing-Taussig syndrome is better tolerated than other types of transposition (Martin and Lewis 1953), and Case II illustrates this well. The history in this child suggests that cyanosis may not be a distinctive symptom until at least one year of age. The differential diagnosis from Eisenmenger's syndrome may be made partially at least by the later onset of cyanosis in that condition. Angiocardiography is probably the best method of definitive diagnosis in the Taussig-Bing syndrome since the levoposition of the pulmonary artery is readily demonstrable.

In contradistinction to Taussig's (1949) opinion, angiocardiography was well tolerated by these two cases. This is confirmed by the lack of complication noted by the authors already cited.

SUMMARY

Two further cases of Bing-Taussig syndrome are presented. The diagnosis was established by angiocardiography in both instances, and confirmed at autopsy in one. The association of an aortic coarctation in one of these children has not previously been described and gave rise to a curious clinical condition.

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Plasma Cell Leukemia or Multiple Myeloma with Osteosclerosis*

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THE case reported herein is an unusual instance of multiple myeloma or plasma cell leukemia associated with marked osteosclerosis. Myeloma cells were present in the peripheral blood, a finding first reported in 1906 by Gluzinski and Reichenstein[1] and since then recorded by many others. Morrisette and Watkins[2] of the Mayo Clinic, for example, after a careful search of peripheral blood smears observed this phenomenon in forty-one of fifty-six cases. However, in 1947 Lichtenstein and Jaffe[3] were able to report this observation in only two of thirty-five cases. The case recorded here is the only instance of a similar nature in nine cases observed in the past eight years at our hospital.

FIG. 1. Roentgenogram of lower spine showing density of osseous structures.

The severe osteosclerosis observed in this case appears to be quite unique, since a careful review of the literature of the past twenty years fails to disclose a similar observation. In our material the patient reported is the only example of non-typical osseous changes observed. No punched-out areas were seen. However, compression fractures of the fifth and sixth thoracic vertebrae were also noted.

The patient, a sixty-eight year old white male, was first admitted to Mount Vernon Hospital December 20, 1952, with the chief complaint of pain in the back and both hips of three months' duration. The pain was described as constant, and most severe when he was physically active. There was no history of fall or trauma. He was a retired employee of a New York City railway system. On admission, physical examination was essentially negative except for a possible indistinct midline lower abdominal mass. Laboratory data revealed a marked anemia of 8.6 gm. of hemoglobin and 3.0 million erythrocytes per cu. mm., with 19,000 leukocytes per cu. mm. Urine examination was negative. The serum alkaline phosphatase was normal, 4.1 Bodansky units. Blood glucose and non-protein nitrogen were normal. A routine x-ray investigation of the genitourinary tract, chest and pelvis revealed a marked increase in density of the skeleton visualized. (Fig. 1.) The interpreter suggested that the skeletal findings were "consistent with osteoblastic cancer metastases." Further x-ray studies of the gastrointestinal and genitourinary tracts for possible primary malignancy were negative. The patient was discharged as unimproved.

He was readmitted on September 10, 1953, because of marked pallor. He had been feeling

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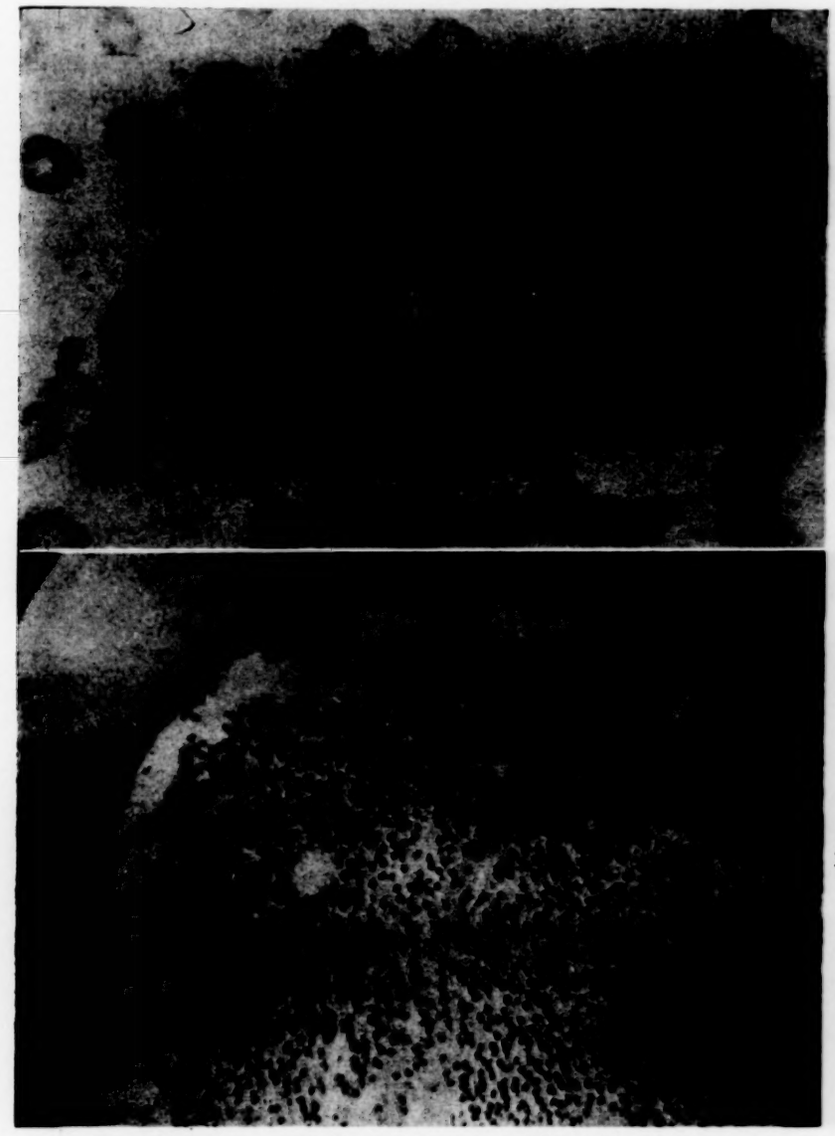

FIG. 2. Typical myeloma cells observed in the peripheral blood smears.

FIG. 3. Sternum biopsy showing uniformity of the small myeloma cells replacing the normal marrow.

well since his last admission, the back pain having been entirely relieved. Physical examination at this time was again negative except for the observed pallor. At this time a hemogram revealed 4.2 gm. of hemoglobin and 1.8 million erythrocytes per cu. mm., and a leukocyte count of 16,000 per cu. mm. The differential blood smear, however, revealed 32 per cent abnormal plasma cells or myeloma cells. (Fig. 2.) The urine at this time showed 2 plus albumin and the presence of Bence-Jones protein. Total serum proteins were 10.8 gm. with albumin 2.8 gm. and globulin 8.0 gm. Serum acid and alkaline phosphatases, calcium and phosphorus were normal. Sternal and iliac crest marrow aspirations were attempted without success. The bone could only be penetrated with great difficulty; the marrow could not be aspirated. A sternal bone biopsy was resorted to. (Fig. 3.) This revealed many small cells with small, round, hyperchromatic nuclei of fairly uniform appearance throughout the marrow. These were interpreted as atypical plasma cells. The osseous tissue was markedly sclerotic, extremely dense with small lacunae and no osteoblastic activity. An x-ray skeletal survey was performed. The

latter revealed diffuse osteosclerosis with some compression of the fifth and sixth vertebral bodies. No typical punched-out areas were seen. The patient has been maintained moderately comfortable with repeated blood transfusions and urethane therapy.

COMMENTS

The observation of osteosclerosis, as well as myeloma cells in the peripheral blood, in an otherwise straightforward case of multiple myeloma raises the question of whether this case should be considered as really one of plasma cell leukemia. Osteosclerosis as an associated finding in leukemia has been mentioned by Chapman[4] who cited case material reported by Mozer, Sternberg, Schmorl, Hueck and Goodall.

SUMMARY

A case of multiple myeloma associated with osteosclerosis and myeloma cells in the peripheral blood is presented. This is the first known observation of associated osteosclerosis in this disease and suggests that this case, along with some others classified as multiple myeloma, might be examples of plasma cell leukemia.

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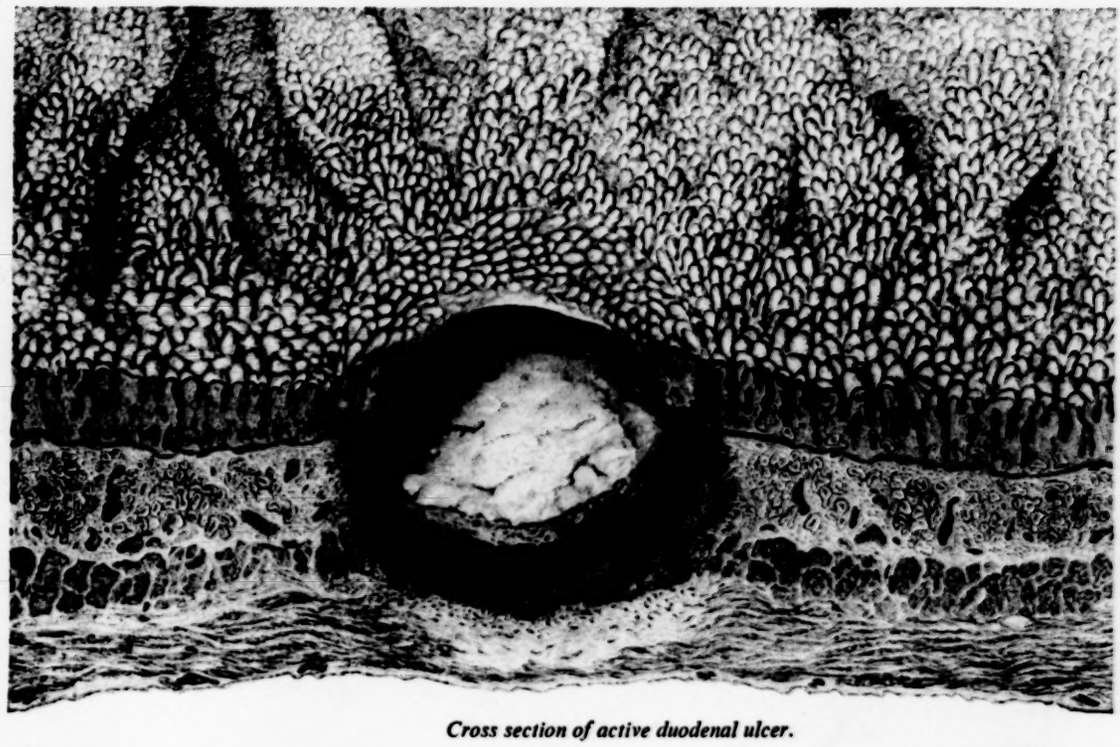

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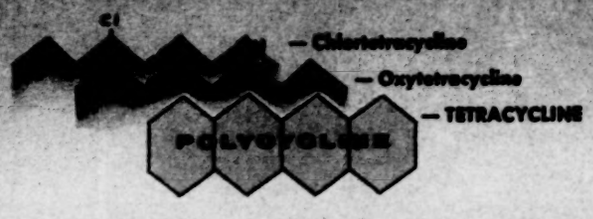

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Surveys show that faulty eating habits largely are responsible for the high incidence of nutritional deficiency and anemia in school children.[3] Among commonplace practices carrying such nutritional hazards are small, poorly chosen breakfasts or omission of the morning meal; the selection of foods left to discretion of the child; overindulgence in foods and drinks providing calories but little of protein, vitamins, and minerals; failure to eat meat or equivalent foods in adequate quantity; and the eating of insufficient amounts of vegetables and fruits.[4]

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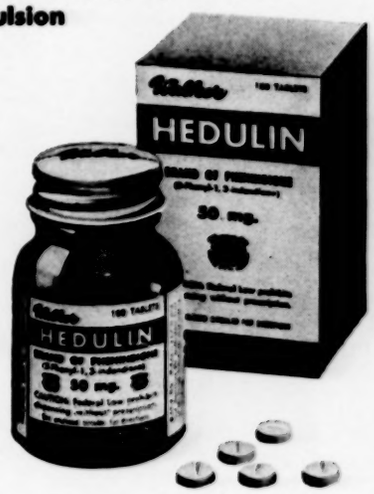

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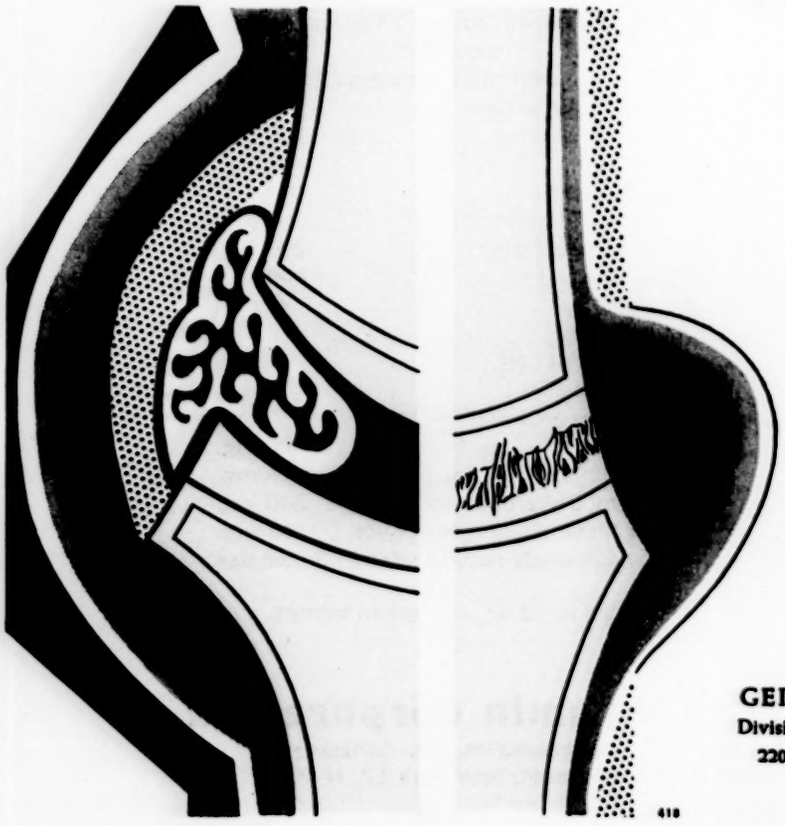

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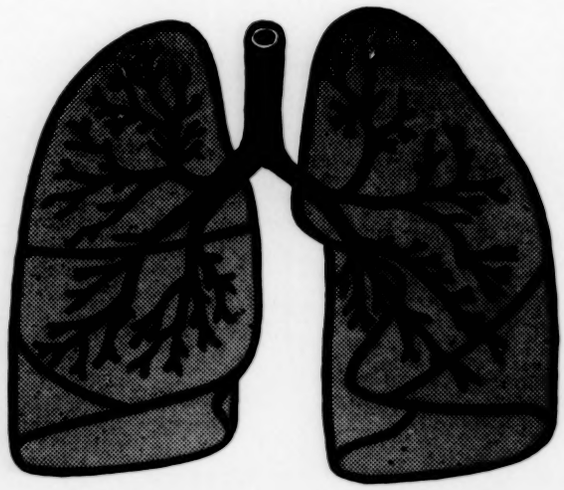

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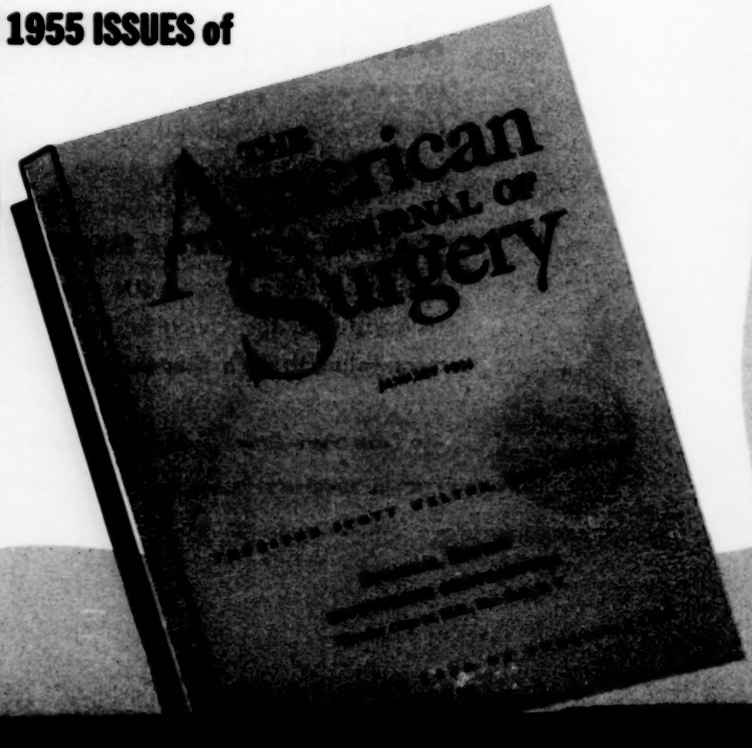

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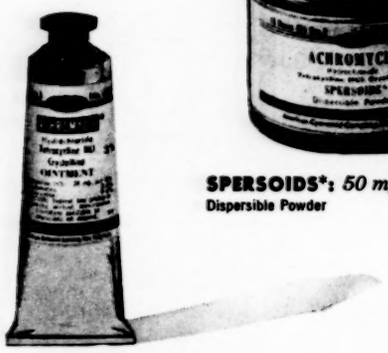

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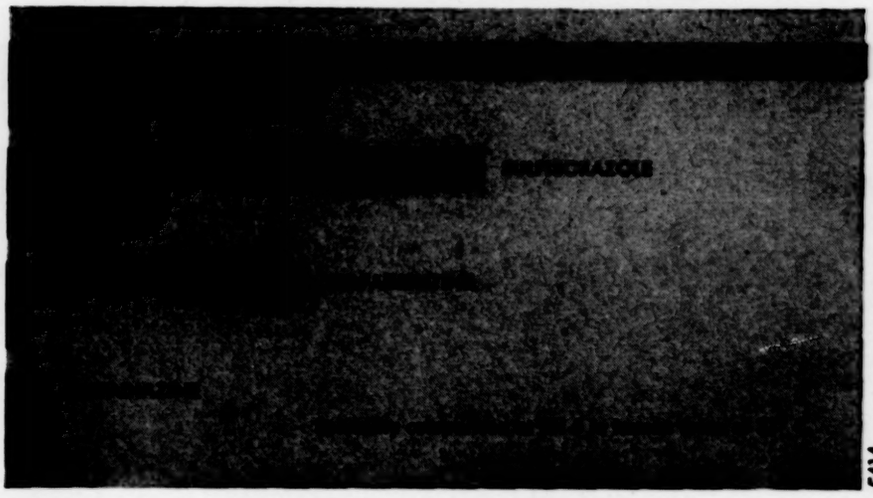

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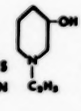

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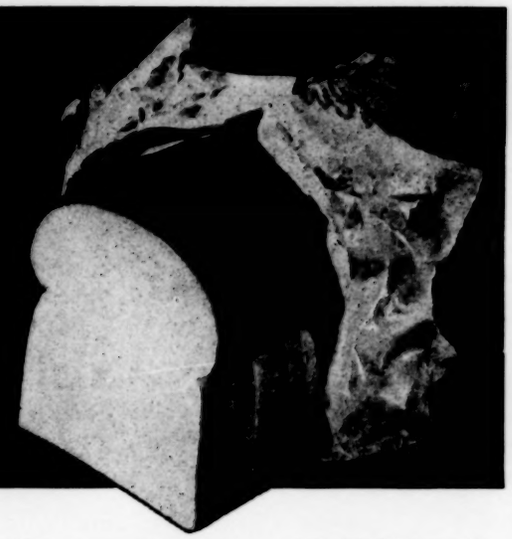

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Supplying 13 grams of high grade protein per 5½ ounces (estimated average daily consumption), enriched bread makes an important contribution to the daily protein need. Its protein, comprising flour, milk, and yeast proteins, functions in the healing of wounds and in the rebuilding of wasted tissues.[2] In addition, 5½ ounces of enriched bread supplies on the average 0.37 mg. of thiamine, 0.23 mg. of riboflavin, 3.4 mg. of niacin, 4.1 mg. of iron, 137 mg. of calcium, and 418 calories.

FOR THE CHRONICALLY ILL...

In the formulation of palatable and nutritious menus for the debilitated, chronically ill, the advantages of enriched bread serve well.

In anorexia, enriched bread or toast stimulates the appetite. It is easily masticated and readily digested, features particularly important for elderly patients. Its favorable textural influence within the alimentary tract[3] promotes good utilization of ingested foods.

---

1. The Committee on Dietetics of the Mayo Clinic: Mayo Clinic Diet Manual, ed. 2, Philadelphia, W. B. Saunders Company, 1954.

2. Sherman, H.C.: Chemistry of Food and Nutrition, ed. 8, New York, The Macmillan Co., 1952, pp. 212, 599.

3. Sherman, H.C.: The Nutritional Improvement of Life, New York, Columbia University Press, 1950, p. 133.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION

20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

THERAPY IN DEPTH

in angina pectoris... status anginosus

PENTOXYLON—combining the tranquilizing, stress-relieving, bradycrotic effects of Rauwiloid® and the prolonged coronary vasodilating effect of pentaerythritol tetranitrate (usually abbreviated PETN)—provides a completeness of treatment heretofore unavailable to angina patients.

Therapy in depth—a wholly new principle in angina therapy—for the first time encompasses effective treatment for cause-and-effect mechanisms, which goes deeper than the superficial plane of relief afforded by simple coronary vasodilatation.

Pentoxylon is not a substitute for nitroglycerin. Continued therapy with Pentoxylon can be expected to reduce markedly or abolish nitroglycerin requirements, and greatly relieve the apprehension of the patient who lives in continuous dread of the next attack.

Each long-acting tablet of Pentoxylon contains pentaerythritol tetranitrate (PETN) 10 mg. and Rauwiloid 1 mg.

Dosage: one to two tablets q.i.d., usually at mealtime and before retiring.

Available in bottles of 100 tablets.

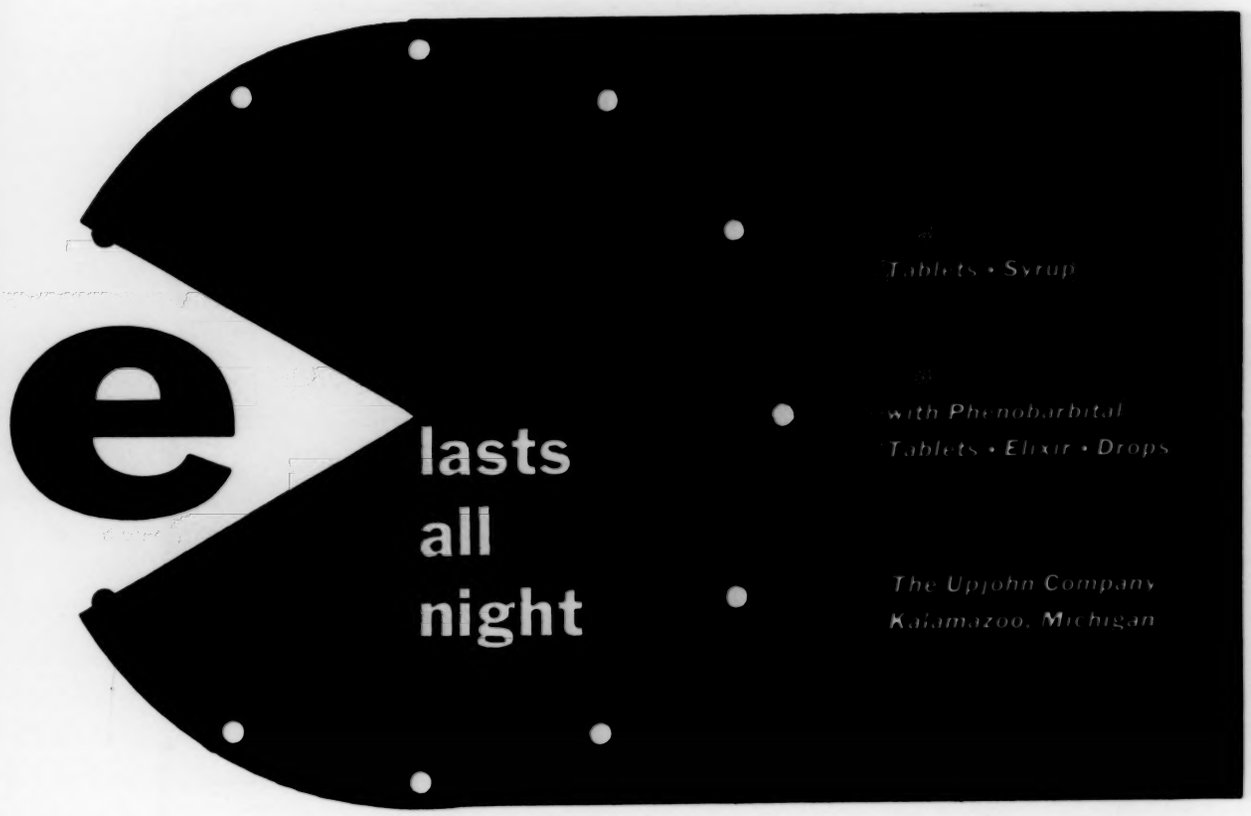
- Reduces nitroglycerin needs
- Reduces severity of attacks
- Reduces incidence of attacks
- Increases exercise tolerance
- Reduces tachycardia
- Reduces anxiety, allays apprehension
- Lowers blood pressure in hypertensives
- Does not lower blood pressure in normotensives
- Produces objective improvement demonstrable by EKG.

Descriptive brochure on request.

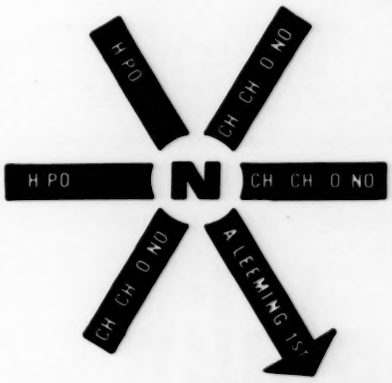
PENTOXYLON™

Another **Riker** *Original*

RIKER LABORATORIES, INC., LOS ANGELES 48, CALIFORNIA



Angina pectoris prevention



The new strategy in angina pectoris is prevention, the new low-dose, long-acting drug—METAMINE. Most effective milligram for milligram, and better tolerated, METAMINE prevents attacks or greatly diminishes their number and severity. *Dosage:* 1 tablet (2 mg.) after each meal; 1-2 tablets at bedtime.

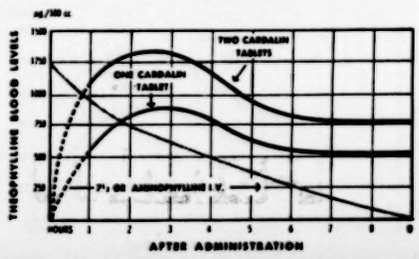
Thos. Leeming & Co. Inc.

155 EAST 44TH STREET, NEW YORK 17, N.Y.

Metamine®

Triethanolamine trinitrate biphosphate, Leeming, tablets 2 mg.

Bottles of 50 and 500.



Sustained plasma theophylline levels were higher with 1 or 2 oral Cardalin tablets than with 7½ gr. of aminophylline I. V.
(Adapted from Bickerman, H.A., et al.: Ann. Allergy 11: 301, 1953, and Truitt, E.B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100: 309, 1950.)

Cardalin's HIGH BLOOD LEVELS

produce these outstanding results in bronchospastic crises

RESULTS IN THERAPY	REFERENCES
Continued relief of paroxysms of bronchospasm.	Segal, M.S., et al.: Quart. Rev. Allergy & Applied Immunol. 6: 399, 1952.
Effective, continuous bronchodilatation.	Levine, E.R., Med. Rec. & Ann. 46: 332, 1952.
Higher aminophylline blood levels (above 0.5 mg. %) obtained for relief of persistent bronchospasm.	Segal, M.S., and Dulfano, M.J.: GP 7: 58, 1953.
Produces productive coughing following bronchodilatation.	Barach, A.L., et al.: Dis. Chest 23: 121, 1953.
Excellent increases in vital capacity and maximum breathing capacity.	Bickerman, H.A., et al.: Ann. Allergy 11: 309, 1953.
Prevention of bronchospastic crises, control of dyspnea and orthopnea.	Segal, M.S., and Dulfano, M.J.: Chronic Pulmonary Emphysema. Mod. Med. Monographs, New York, Grune & Stratton, 1953, No. 8, pp. 79-80.

Each Cardalin tablet contains:

Aminophylline . . . . . 5.0 gr.
Aluminum Hydroxide . . . . . 2.5 gr.
Ethyl Aminobenzoate . . . . . 0.5 gr.

Supplied: Bottles of 50, 100, 500, 1000.

Also available, Cardalin-Phen containing ¼ gr. phenobarbital per tablet.

Cardalin tablets

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

For the infections common to the fall of the year to which we all are heir, a prescription of choice among physicians the world over is often

Terramycin®

BRAND OF OXYTETRACYCLINE

Worldwide experience over many years has established this well-tolerated, promptly effective, broad-spectrum antibiotic as an agent of choice in the treatment of infections due to susceptible gram-positive and gram-negative bacteria, rickettsiae, spirochetes, certain large viruses and protozoa.

Supplied in convenient dosage forms required for individualized regimens: Terramycin Capsules, Tablets *(sugar coated)*, Pediatric Drops, Oral Suspension, Intravenous, Intramuscular, Ophthalmic *(for solution)*, Ophthalmic Ointment, Ointment *(topical)*, Vaginal Tablets, Troches, Otic, Nasal, Aerosol, Soluble Tablets and Topical Powder.

Pfizer

PFIZER LABORATORIES, Brooklyn 6, N.Y.
Division, Chas. Pfizer & Co., Inc.

Meets

U.S.P. SPECIFICATIONS FOR VITAMIN B_{12} WITH INTRINSIC FACTOR CONCENTRATE

1 U.S.P. Unit in recommended daily dosage

Plus

75 MCG. OF B_{12} (in addition to 1 U.S.P. Unit in recommended daily dosage)

PATTERNED AFTER

*Spies' Basic Formula**

Provides Vitamin C, Folic Acid, Thiamine, Riboflavin, and Nicotinamide, in addition to increased amounts of B_{12}

*Spies, T. D., J.A.M.A. 145:66 (Jan. 13) 1951.

"CLUSINTRIN"

Potent Hematinic for effective, practical Antianemia Therapy

Each capsule contains:

Vitamin B_{12} with intrinsic factor concentrate	0.33 U.S.P. Unit
Vitamin B_{12} U.S.P. (crystalline)	25.0 mcg.
Folic acid U.S.P.	1.67 mg.
Vitamin C (ascorbic acid)	50.0 mg.
Thiamine mononitrate (B_1)	3.34 mg.
Riboflavin (B_2)	3.34 mg.
Nicotinamide	50.0 mg.
Ferrous sulfate exsic.	200.0 mg.

No. 316 — Supplied in bottles of 100 and 1,000.

Indications: Treatment of pernicious anemia and other macrocytic hyperchromic anemias; microcytic hypochromic anemia.

Recommended dosage: 1 capsule three times daily, or as required. Preferably taken after meals.

Ayerst

5449

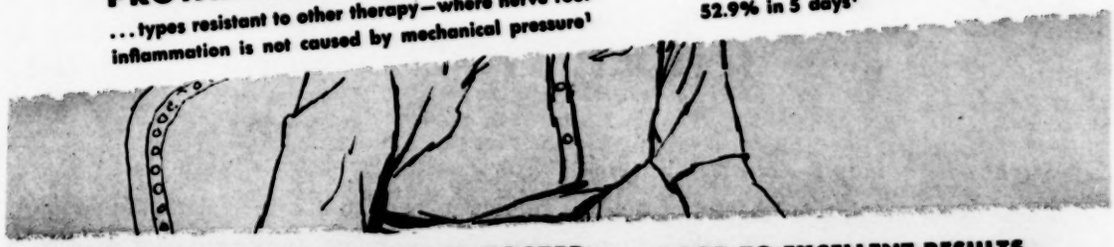
AYERST LABORATORIES • New York, N. Y. • Montreal, Canada

PROTAMIDE® for NEURITIS

...types resistant to other therapy—where nerve root inflammation is not caused by mechanical pressure[1]

COMPLETE RELIEF OF PAIN

in 80.7% of patients...
52.9% in 5 days[1]

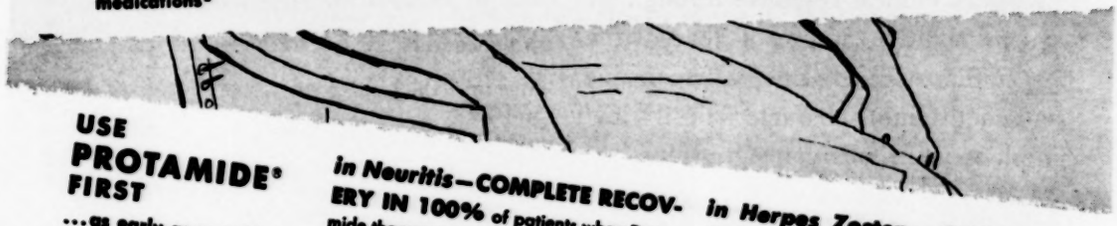


PROTAMIDE® for HERPES ZOSTER

...even cases unresponsive to a wide variety of other medications[2]

GOOD TO EXCELLENT RESULTS

in 82.7% of patients in two studies...
70.4% with 5 injections or less[2,3]

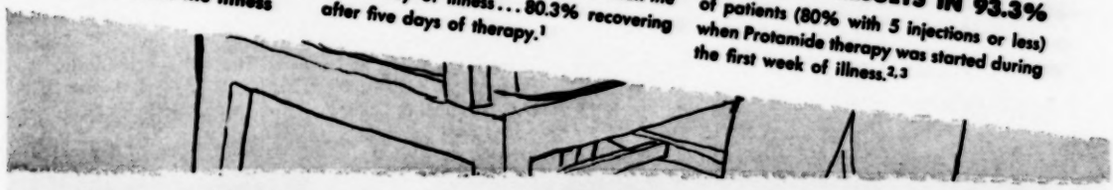


USE PROTAMIDE® FIRST

...as early as possible in the course of the illness

***in Neuritis*—COMPLETE RECOVERY IN 100%** of patients when Protamide therapy was started not later than the fourth day of illness... 80.3% recovering after five days of therapy.[1]

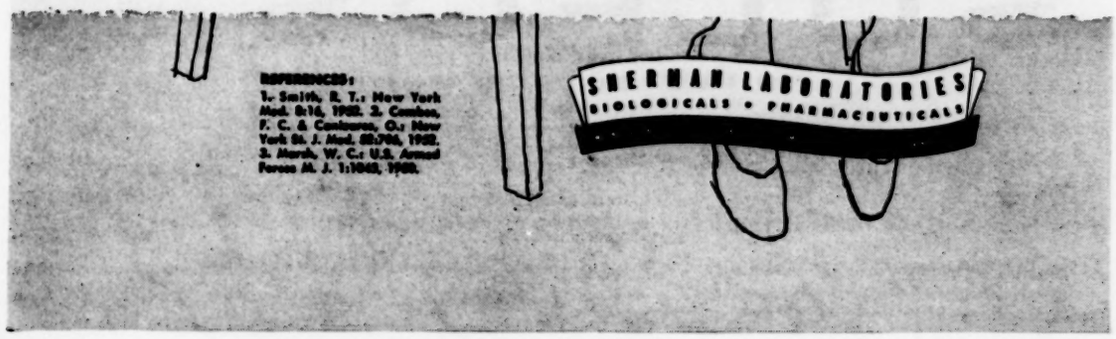
***in Herpes Zoster*—GOOD TO EXCELLENT RESULTS IN 93.3%** of patients (80% with 5 injections or less) when Protamide therapy was started during the first week of illness.[2,3]



PROTAMIDE® IS SAFE

with "no untoward reactions or evidence of toxicity"[2]

PROTAMIDE is a sterile colloidal solution of processed and denatured proteolytic enzyme obtained from the glandular layer of fresh hog stomach. It is supplied in boxes of ten 1.3 cc. ampuls, and the usual dosage is 1 ampul daily by intramuscular injection. Available through your regular source of supply.



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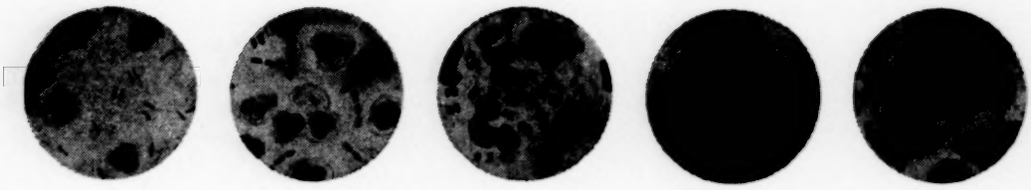
1. Smith, R. T.: New York Med. 8:16, 1952. 2. Comben, F. C. & Comben, O.: New York St. J. Med. 52:706, 1952. 3. Marsh, W. C.: U.S. Armed Forces M. J. 1:1043, 1950.

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS



IN URINARY-TRACT INFECTIONS

High where height counts,[1] SULFOSE blood levels foster antibacterial action where therapy counts—*within* the infected tissue of the urinary system.[2] For SULFOSE promotes clinical response through the potent additive attack of three sulfapyrimidines (sulfadiazine, sulfamerazine, sulfamethazine), characteristically high in blood and tissue concentrations.

Low where lowness counts, SULFOSE is low in toxicity, low in renal risk . . . provides three independent sulfonamide solubilities for protection against crystalluria.[3]

Suspension SULFOSE—triple sulfonamides suspended in a special *alumina gel* base for complete dispersion and ready absorption. Indicated in all infections due to sulfonamide-sensitive organisms.

Supplied: Suspension SULFOSE, bottles of 1 pint

Also available: Tablets SULFOSE, bottles of 100 and 1000

Each teaspoonful (5 cc.) of Suspension and each Tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine, and sulfamethazine

1. Jawetz, E.: California Med. 79:99 (Aug.) 1953. 2. Cecil, R.L., and Loeb, R.F.: Textbook of Medicine, W. B. Saunders Co., Philadelphia, 1951, pp. 963-967. 3. Sophian, L.H., and others: The Sulfapyrimidines, Press of A. Colish, New York, 1952. 4. Berkowitz, D.: Antibiot. & Chemo. 3:618 (June) 1953.

FOR SUPERIOR BLOOD LEVELS[4]

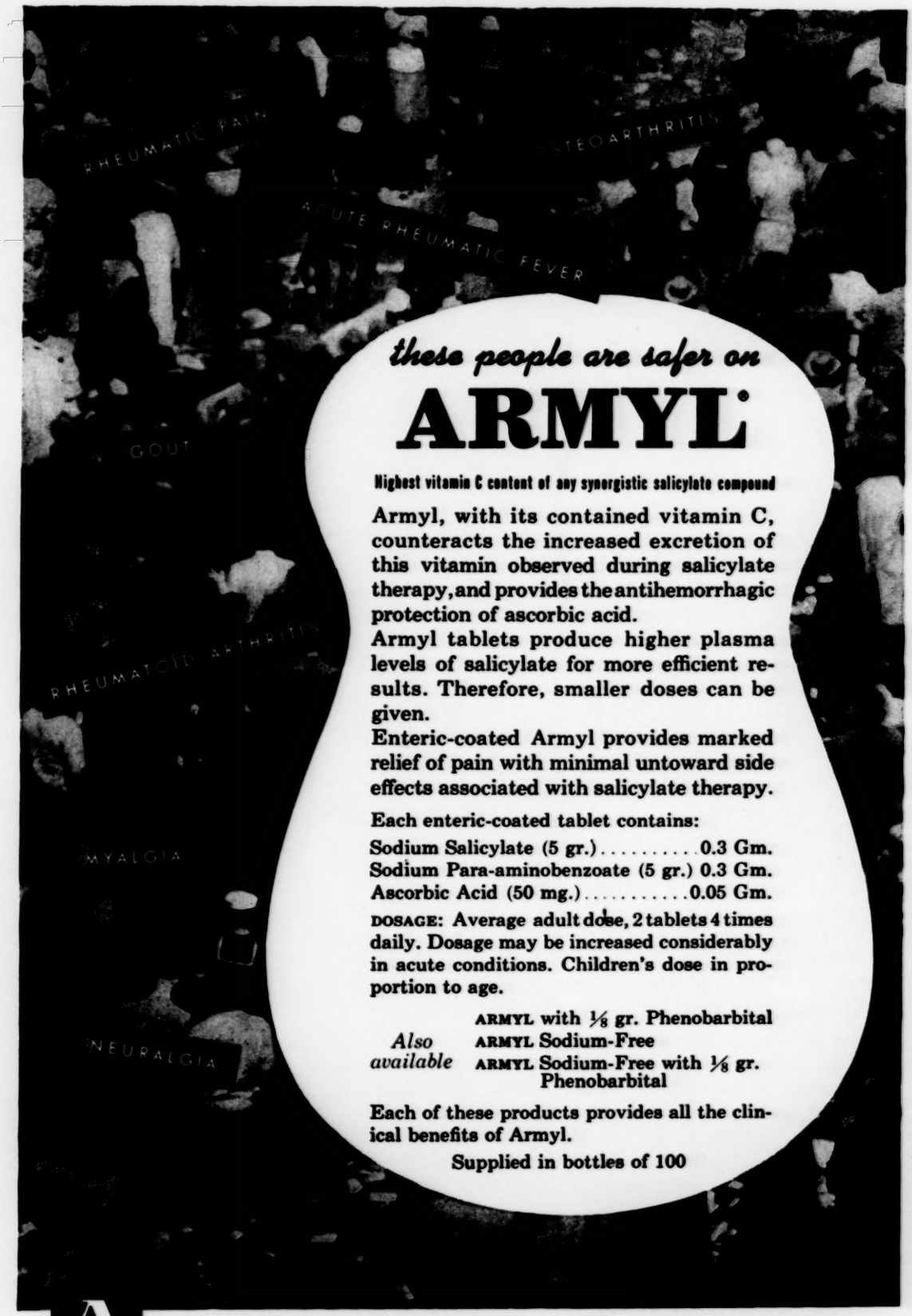
SUSPENSION

SULFOSE®

TRIPLE SULFONAMIDES

Wyeth®

Philadelphia 2, Pa.



these people are safer on

ARMYL®

Highest vitamin C content of any synergistic salicylate compound

Armyl, with its contained vitamin C, counteracts the increased excretion of this vitamin observed during salicylate therapy, and provides the antihemorrhagic protection of ascorbic acid.

Armyl tablets produce higher plasma levels of salicylate for more efficient results. Therefore, smaller doses can be given.

Enteric-coated Armyl provides marked relief of pain with minimal untoward side effects associated with salicylate therapy.

Each enteric-coated tablet contains:

Sodium Salicylate (5 gr.).....0.3 Gm.
Sodium Para-aminobenzoate (5 gr.) 0.3 Gm.
Ascorbic Acid (50 mg.).....0.05 Gm.

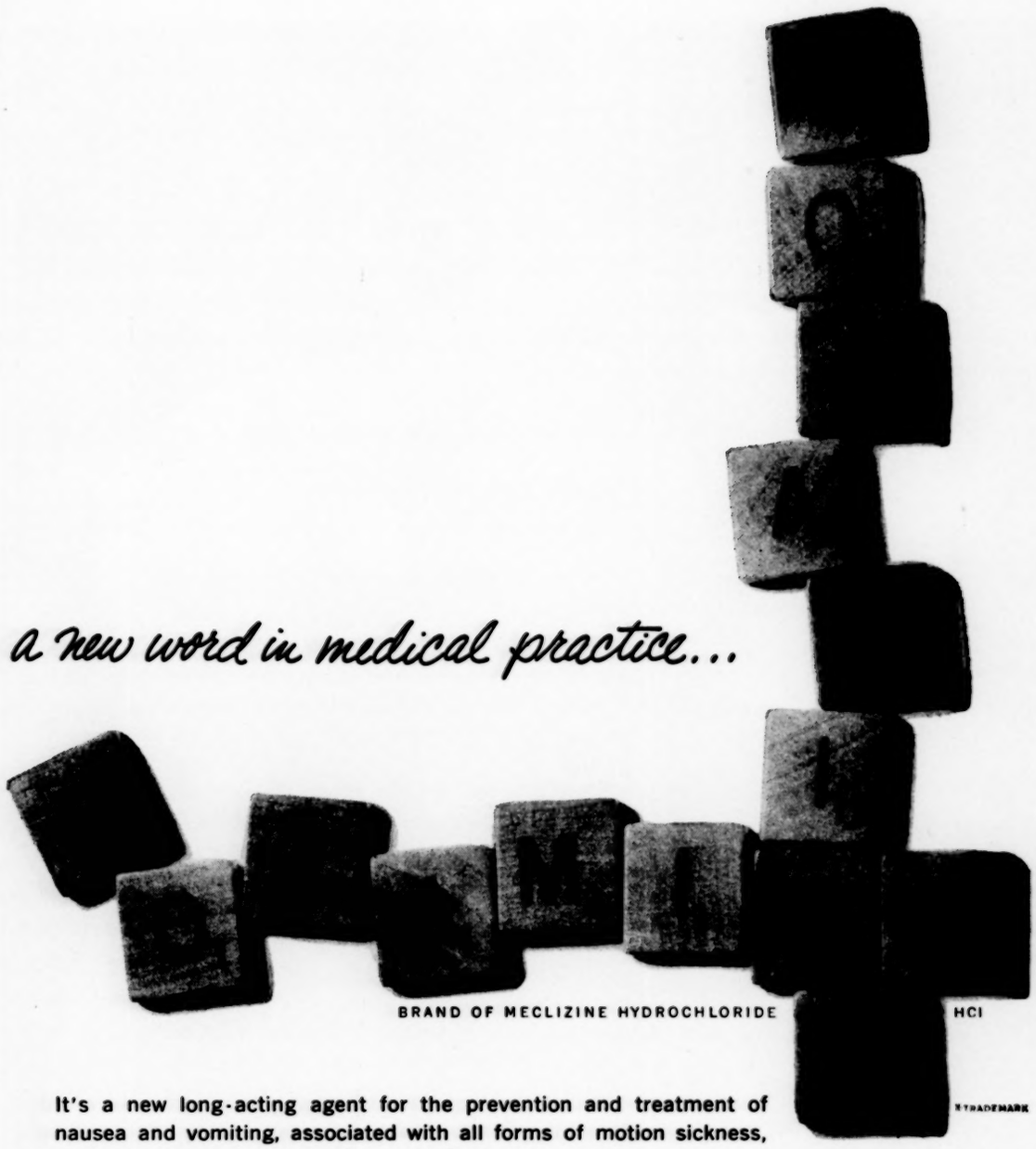
DOSAGE: Average adult dose, 2 tablets 4 times daily. Dosage may be increased considerably in acute conditions. Children's dose in proportion to age.

Also available
ARMYL with 1/8 gr. Phenobarbital
ARMYL Sodium-Free
ARMYL Sodium-Free with 1/8 gr. Phenobarbital

Each of these products provides all the clinical benefits of Armyl.

Supplied in bottles of 100

THE ARMOUR LABORATORIES A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS



a new word in medical practice...

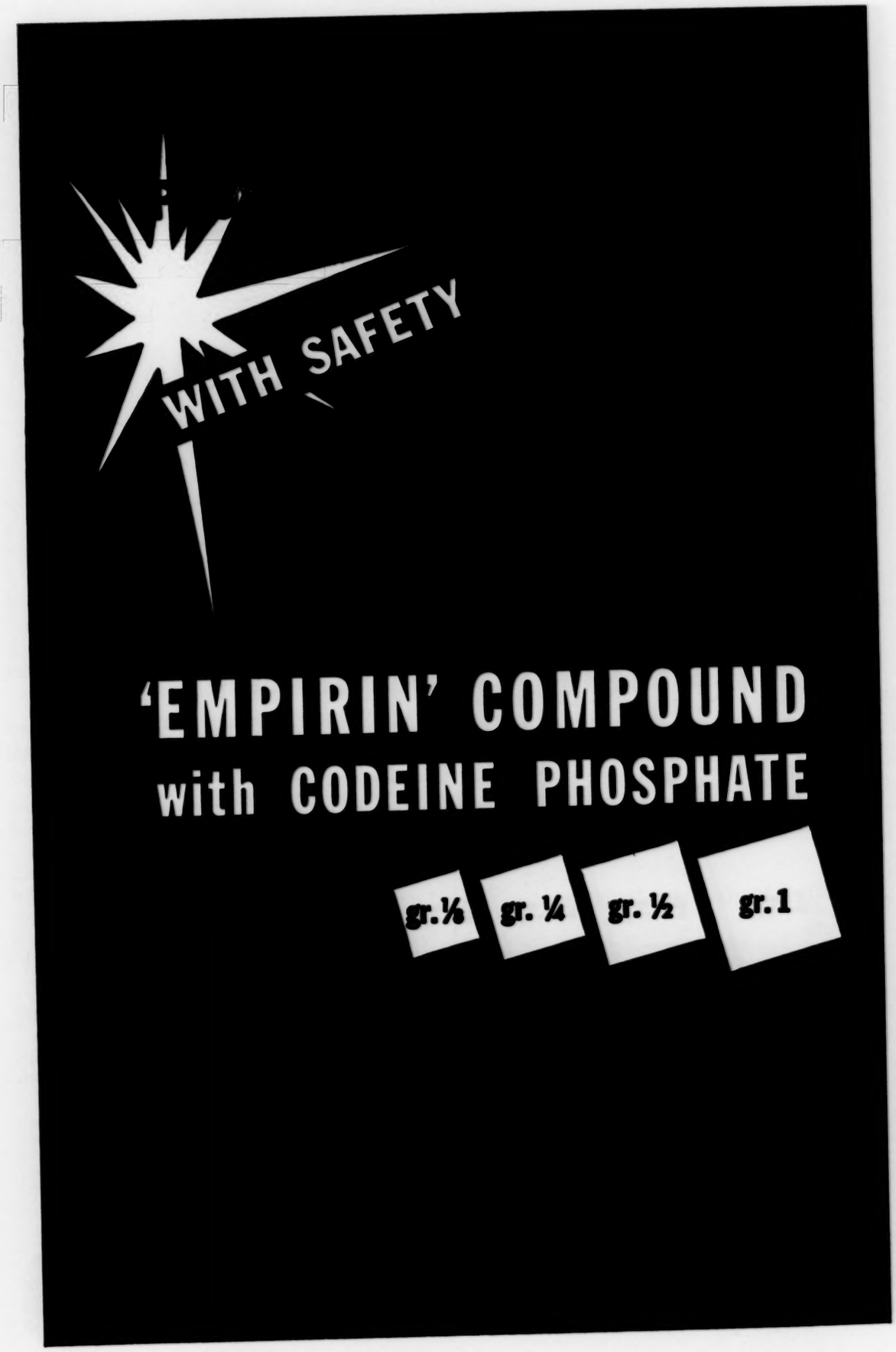
BRAND OF MECLIZINE HYDROCHLORIDE HCl

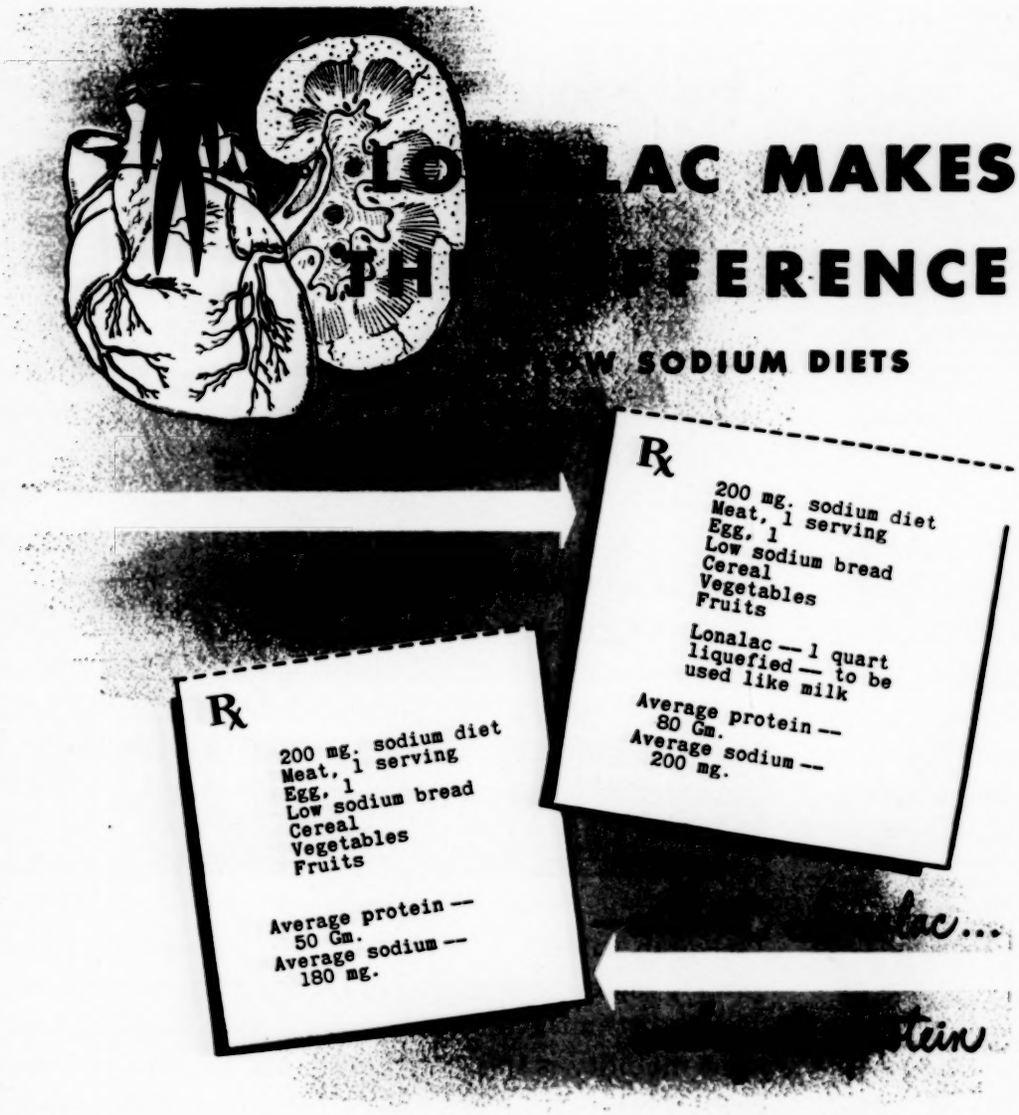
®TRADEMARK

It's a new long-acting agent for the prevention and treatment of nausea and vomiting, associated with all forms of motion sickness, radiation therapy, vestibular and labyrinthine disturbances, and Ménière's syndrome.

Side effects, so often associated with the use of earlier remedies, are minimal with Bonamine. Its duration of action is so prolonged that often a single daily dose is sufficient. Bonamine is supplied in scored, tasteless 25 mg. tablets, boxes of eight individually foil-wrapped and bottles of 100.

PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.


WITH SAFETY
'EMPIRIN' COMPOUND
with CODEINE PHOSPHATE
gr. ⅛
gr. ¼
gr. ½
gr. 1



Nutritionally similar to whole milk but with negligible sodium content, Lonalac solves the problem created by the high sodium content of the usual protein foods.

When sodium intake must be sharply restricted, protein deficiency is seriously threatened . . . since meat and eggs can be used only in small quantities and milk, with its still higher sodium content, usually must be eliminated.

With Lonalac supplying the protein equivalent of milk, the patient's nutritional needs can be generously met, even on a 200 mg. sodium diet.

Lonalac is used just as milk is used, as a beverage and in soups, muffins, desserts, etc. It permits varied and appetizing meals that encourage patients to adhere to a low sodium regimen.

Lonalac is virtually free of cholesterol.

Lonalac is supplied in 1 pound and economical 4 pound cans. Low sodium diet outlines suitable for use by patients are available on request.

Lonalac

The low sodium, high protein food

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD

CLINICAL REPORT ON ANSOLYSEN . . .
NEW ANTIHYPERTENSIVE AGENT

ANSOLYSEN—pentolinium tartrate—is a potent ganglionic blocking agent which presents the advantage of comparative freedom from by-effects. This effective hypotensive agent is recommended for use in patients with moderate to severe hypertension.

Comparing the effects of hexamethonium and ANSOLYSEN in 27 patients with severe "fixed" hypertension, Freis and coworkers[1] observed:

ANSOLYSEN was approximately five times more potent than hexamethonium

ANSOLYSEN produced less tolerance

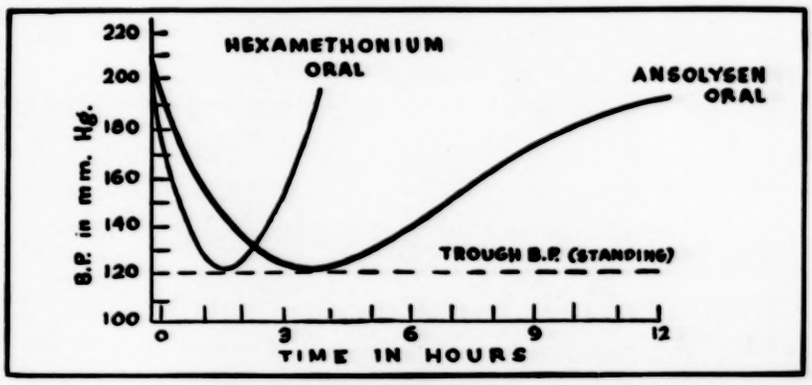
ANSOLYSEN's hypotensive effect was 40% longer

ANSOLYSEN's hypotensive effect was more predictable

ANSOLYSEN caused less pronounced by-effects

ANSOLYSEN caused less constipation

ANSOLYSEN lowered the blood pressure significantly, with little or no risk of producing collapse reactions or paralytic ileus



Changes in blood pressure noted by Smirk[2] after therapeutic oral doses of hexamethonium and ANSOLYSEN.

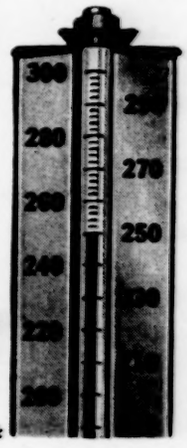
Supplied: Scored tablets—40 and 100 mg., bottles of 100
Injection—10 mg. per cc., vials of 10 cc.

1. Freis, E. D., and others: Circulation 9:540 (April) 1954
2. Smirk, F.H.: New Zealand M.J. 52:1 (Oct.) 1953

ANSOLYSEN*

PENTOLINIUM TARTRATE

*Trademark



Wyeth®
Philadelphia 2, Pa.

FOR IRON-DEFICIENCY AND NUTRITIONAL ANEMIAS

Iberol® is iron-*plus*

just 3 tablets a day supply:

ferrous sulfate, U.S.P..... 1.05 gm.
(210 mg. of elemental iron)

+

stomach-liver digest..... 1.5 gm.
(containing intrinsic factor)

+

ascorbic acid..... 150 mg.

+

vitamin b_{12}..... 30 mcg.
folic acid..... 3.6 mg.
thiamine mononitrate..... 6 mg.
riboflavin..... 6 mg.
nicotinamide..... 30 mg.
pyridoxine hydrochloride.... 3 mg.
pantothenic acid..... 6 mg.

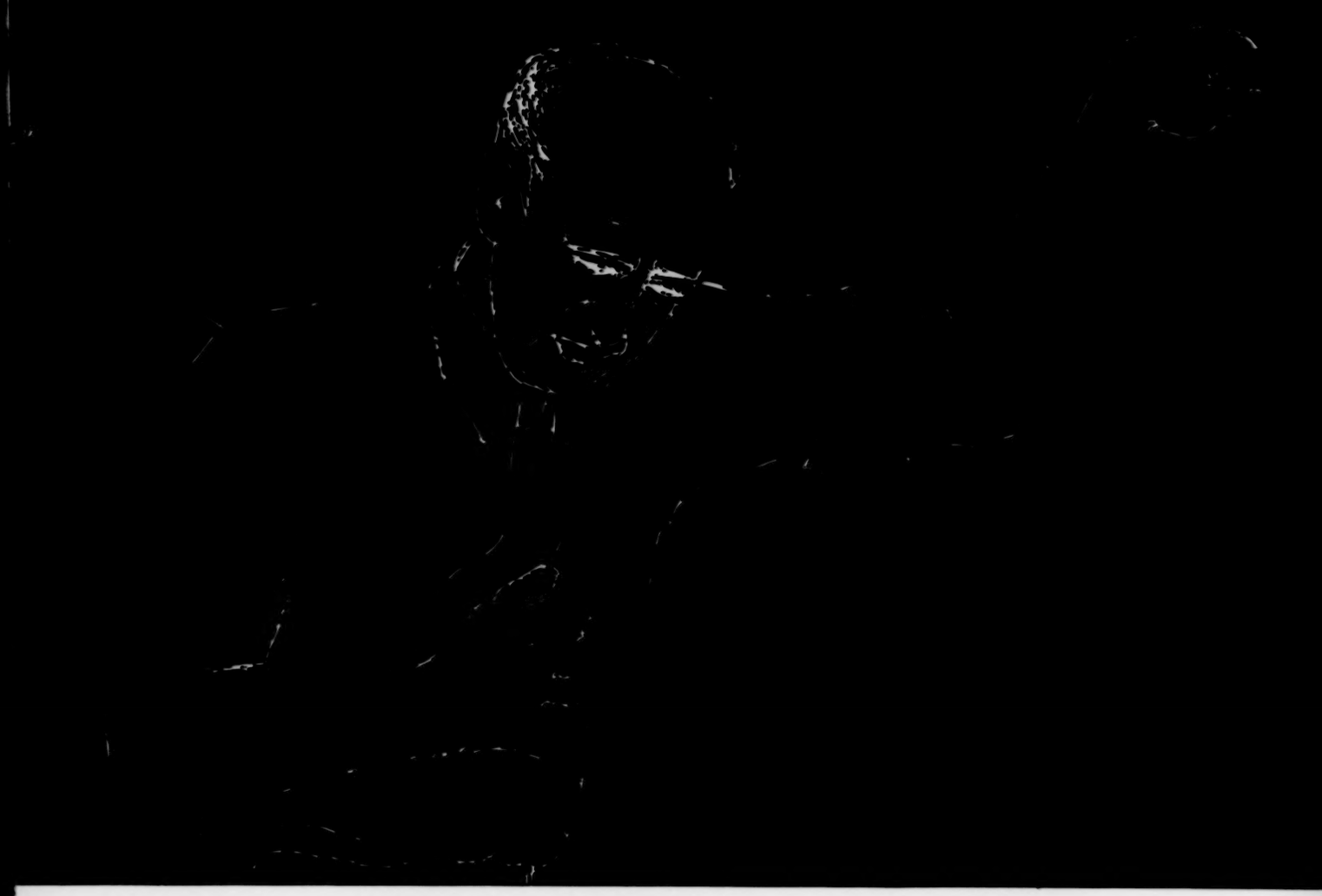
the right amount of iron

plus complete B complex

Abbott

a pleasant-tasting tablet, not a capsule

410161



You can prevent attacks in angina pectoris

Prolonged prophylaxis

Patients receiving Peritrate may obtain practical freedom from anginal attacks for from 4 to 5 hours with each dose. Russek and his colleagues[1] clearly showed that the patient-response to Peritrate was comparable to the effect produced by nitroglycerin . . . *but* the duration of Peritrate's action was ". . . *considerably more prolonged.*"

Uncomplicated prophylaxi

Prolonged protection given by Peritrate spares the patient the anxiety of waiting for pain to strike. Besides invaluable psychological support, Peritrate brightens the objective clinical picture —significant EKG improvement may be seen[1,2] and nitroglycerin need greatly reduced in most.[3] A continuing schedule of only 1-2 tablets four times a day, before meals and at bedtime, will:

1. *reduce the number of attacks in almost 80 per cent of patients*[2,3]
2. *reduce the severity of attacks which cannot be prevented.*

Available in 10 mg. tablets in bottles of 100, 500 and 5000.

References:

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.

Peritrate®

tetranitrate

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT